

THE POLYNEURITIC SYNDROME

Its aetiological relationship to Nutrition and
its association with Vitamin B₁ deficiency.

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FRANK AYREY, M.B., Ch.B.



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INTRODUCTION.

In 1787, J. C. Lettsom¹ first described Alcoholic Polyneuritis. Until recently the belief that spirituous liquor possessed a direct toxic action on nerve tissue has been rigorously observed. Polyneuritis is also associated with a multitudinous number of poisons and toxins, known and unknown, endogenous and exogenous. These too, have been thought to exert a direct neurotoxic action similar to that of alcohol.

Recently, however, the close similarity between the clinical and pathological manifestations of alcoholic polyneuritis and the disease Beri-beri was observed. The parallel was drawn closer by the fact that aetiological study of a group of patients suffering from alcoholic polyneuritis revealed a prolonged deficiency of vitamin B₁. These patients were cured without withholding their customary supplies of alcohol, and the main therapeutic agent employed was an adequate diet with abundance of vitamin B₁.

Similarly, cases of Gestational Polyneuritis have successfully responded to treatment directed to the repair of deficiencies without the pregnancies being prematurely terminated. The result has been to raise

serious doubts as to whether alcohol and the hypothetical toxins of pregnancy function as direct neurotoxic agents.

If we consider for a moment the number and diversity of conditions with which polyneuritis is associated, then similar doubts must obviously exist as to the polyneuritis being a specific expression of such a multitudinous number of toxins. The pathological degenerative changes in the peripheral nerves are identical; the early clinical phenomena very similar. On the other hand, the aetiological factors of deficiency are obscure and have not in fact been adequately investigated. Interest has been stimulated in these problems by numerous reports in the literature testifying to the efficacy of vitamin B₁ as a therapeutic agent in many cases of classified and unclassified polyneuritis. If we accept these results and those achieved in alcoholic and gestational polyneuritis as being due to the administration of vitamin B₁, and if we grant that Beri-beri is fundamentally due to a deficiency of the same vitamin, then we are driven to the conclusion that these cases of polyneuritis represent a fragment, at least, of beri-beri itself. And we are justified in seeking evidence of the same

aetiological factor in these cases - a failure of adequate intake, or absorption, of the antineuritic vitamin.

Such a quest receives encouragement from certain newer conceptions that have been granted to students of medicine in recent years. We now know that beri-beri is no more confined to rice-eating peoples than pellagra is to maize-eaters. Both are recognised deficiency diseases, but it is an accepted fact that both conditions can and do occur in any individual or community where there is a gross or prolonged inadequacy of the accessory food factors concerned. The old belief, "What pellagra is to maize, beri-beri is to rice" has been rightly discarded. Again, the number of syndromes recognised as being due to deficiencies of all kinds is increasing, whether these deficiencies be extrinsic or intrinsic factors, vitamins, hormones or minerals. While we are alive to the significance of gross diseases such as rickets, scurvy, beri-beri and pellagra, we are also willing to realise that many minor degrees of ill-health may result from prolonged partial deficiencies of the same vitamin factors. In short, we are appreciating more and more that disease may be associated with minus signs no less than positive

ones - the toxin, the bacterium, the parasite. The combination of derangements of the haemopoietic, neurological and gastro-intestinal systems is leading to more thorough investigation of the factors which must influence this linkage; the combination of pernicious anaemia, subacute combined degeneration of the spinal cord and achylia gastrica, and the occurrence of mental, nervous and anaemic manifestations in achlorhydric pellagra may be cited in this connection.

Bearing in mind these various conceptions, an investigation of the aetiological factors operating as deficiencies in cases of polyneuritis seemed justifiable. It was deemed advisable first to study the available data referable to the disease beri-beri, and the part played by vitamin B₁ in the production of the various pathological, metabolic and clinical manifestations, so that some degree of correlation would be possible.

There is no attempt made here to elucidate the aetiology of all forms of polyneuritis or to prove that these cases represent veiled beri-beri. The investigation was undertaken to determine whether a vitamin B₁ deficiency could be shown to operate as an aetiological factor in a series of cases of polyneuritis, and the extent of that involvement, if present. To

some extent therefore the work coincidentally determines the value of vitamin B₁ as a therapeutic agent.

In 1936, brilliant chemical research resulted in the synthesis of vitamin B₁ by workers in Germany and America, and by Drs Todd and Bergel² in Professor Barger's Department in the University of Edinburgh. Dr Ritchie Russell³ was a pioneer of the parenteral method of administration of this product in the wards of the Royal Infirmary and published his results following treatment of several cases of polyneuritis. These were so encouraging as to warrant a detailed study of further cases. I was privileged to collaborate with Dr Russell in the investigation and the results and conclusions drawn furnish the basis of this thesis. No attempt was made to choose suitable or classified cases. Any and every case manifesting polyneuritic symptoms and signs was investigated and treated. I have not presumed, therefore, to offer an elucidation of the aetiology of any particular form of polyneuritis. In fact most of the cases will be seen to belong to the group designated 'of unknown origin'. But, as I think the large body of practitioners of medicine will agree that by far the greater majority of polyneuritic cases fall into the latter category, any

value the work possesses should not lose on this account. At the same time the conclusions drawn from the present investigation and a study of other cases quoted in the literature, have encouraged me to take the liberty of tentatively suggesting aetiological factors which may apply to many other forms of polyneuritis, other than those studied.

This work affords convincing proof of the many fields of investigation awaiting further study before the elucidation of polyneuritis and many other neurological syndromes is achieved. But I am equally convinced that the application of the "deficiency hypothesis" to these problems affords a fascinating field of study, in the exploration of which much of value will eventually emerge.

POLYNEURITIS: A General Survey.

Polyneuritis (Multiple Neuritis, Peripheral Neuritis) is usually defined as a condition characterised by degeneration of multiple peripheral nerves, resulting in disturbance of motor and sensory functions, usually affecting the limbs, and of symmetrical distribution.

Whilst the clinical picture is subject to variation according to onset, acuteness, chronicity, severity and the underlying condition with which the polyneuritic symptoms are associated, there is, nevertheless, a fairly typical picture common to most forms of the disorder, and which permits of description.

It is a time-honoured custom in writing a dissertation on a disease or syndrome to discuss the Aetiological factors at an early stage. The present investigation, however, purports to be a discussion of certain aetiological factors in the causation of many forms of polyneuritis, which are, as yet, imperfectly understood. It is doubtful, for example, whether some of the traditionally described "toxic" forms are, in reality, toxic as implied by their respective descriptions. It is in the disease Beri-beri that the combined work of clinicians, pathologists and bio-chemists

has resulted in the elucidation of hitherto obscure aetiological factors, and the polyneuritis of this condition has been closely related to the fundamental vitamin deficiency. These studies, when applied to other forms of polyneuritis are meeting with results calculated to shake profoundly the traditional beliefs in the aetiological factors which have hitherto been regarded as principal causal mechanisms in the production of the neurological manifestations.

For these reasons, therefore, I propose to deal with the aetiology of polyneuritis in my final discussion, and to deal at this stage with a general survey of interesting observations pertinent to an introductory chapter.

It would serve no useful purpose here to revive the old controversy as to the applicability of the term Polyneur-itis to a condition of nerve-elements now generally believed to be of a Degenerative rather than an Inflammatory nature. Though the histo-pathology of many forms of Polyneuritis has not been adequately investigated, so many kinds have been shown to be degenerative that in others where the signs and symptoms are so similar, pathological processes of the same nature are believed to exist.

The condition is usually Multiple, Symmetrical and Peripheral. Whether toxins, poisons, metabolites or other noxious substances may be responsible for the pathological changes, it is a traditional belief that they gain access to the nervous elements where these are least protected. In the greater part of their extent, nerve-elements are covered by a protective myelin sheath; if they are destined to be affected it seems reasonable to assume that they will be most vulnerable to noxious agencies at those positions where they are exposed by lack of myelin, i.e., at the peripheral nerve end-organs (the neuromuscular junction) and at the synapses in the higher reaches of the nervous system. The same process would obtain in the case of exposure of a nerve in a wound. It is therefore significant that the onset of polyneuritis is usually peripheral and referable either to nerve-endings or the higher synapses.

It is also assumed by many authorities that an additional factor operates, and that the peripheral nerve end organs are more vulnerable the farther they are away from their nutritive cells in the central nervous system.

In the case of Diphtheria and Tetanus, local

infection appears to exercise a great influence; the nerves more closely in contact with the wound or original focus of infection are those which show the chief alteration of function.

Thirdly, though the neuritic manifestations may seem to be dependant on general or local distribution to some extent, another factor merits discussion. Just as certain micro-organisms or toxins seem to possess a selective capacity for certain tissues so, in certain forms of polyneuritis, even when there is believed to be a generalised blood intoxication, certain nerve elements appear to sustain the major abrogation of function. Thus may be cited the frequency with which the ciliary mechanism is affected in diphtheria, the ocular and bulbar neurones in botulism, and the motor nerve fibres in plumbism.

The well-known Korsakoff's Syndrome in certain intoxications is an example of co-existing peripheral and central nervous injury - the association of marked cerebral disturbance with peripheral loss of nervous function. This neuritic-psychosis was long ago recorded in association with intoxications due to lead and copper, but has since been noted in many other forms, particularly those due to alcohol and arsenic. Whilst

in both beri-beri and pellagra a similar and possibly analogous association is by no means uncommon, I can find no trace in the literature of the association of Korsakoff's Syndrome with botulism, tetanus or diphtheria.

Wherever the earliest signs of nervous dysfunction are manifest, there seems to be a varying degree of tendency for the process to spread from its starting point with an increasing loss or impairment of function - often with dramatic rapidity. To these ascending or descending forms the term "Landry's Paralysis" has been given. It has been noted as occurring in many forms of polyneuritis, both in plumbism, alcoholism and many of obscure aetiology, a fact which throws some doubt on its claims to being of specific nature.

Though I shall deal with the pathological aspects of polyneuritis in more detail later, it may be pertinent to state here that permanent structural damage is not a concomitant of the disturbed function of the peripheral nerves, though often the severity of the symptoms and signs would suggest it. It is a well-recognised fact that in animals and birds in which polyneuritis has been experimentally produced by diets lacking the anti-neuritic vitamin, to the extent of complete limb or

wing paralysis, complete recovery can take place in a few hours. Similarly, though perhaps not so dramatically, the restoration of function of a paralysed palate in diphtheria is a common clinical experience.

The pathological process, however, may become irreversible; destruction of nerve-elements and degeneration may be so prolonged that recovery of function is rendered impossible - a condition which may be in evidence clinically and corroborated at autopsy.

The extent to which any attendant inflammatory reaction in the region of the degenerative process takes place is a matter of controversy; it is certainly not a constant factor but seems to be present to a variable degree in some of the acute forms of polyneuritis. Inflammatory changes as evidenced by abnormal changes in the cerebro-spinal fluid - increased protein content, coagula, discolouration, increased number of cells, either lymphocytic or polymorphonuclear - have been observed by some investigators. But they are not constant findings and their association with the polyneuritis, per se, is a matter of conjecture. It is, however, commonly believed that the pain evinced by pressure over an affected limb is due to inflammatory exudation of lymphocytes in the connective

tissue spaces surrounding the affected nerves and the muscle fibres supplied by them.

POLYNEURITIS: A Classification.

The results of recent investigation and treatment of certain forms of polyneuritis are bound to lead eventually to a thorough revision of the aetiological factors in all forms of the condition. In the present light of our knowledge, no classification can be considered as more than provisional.

Therefore the following list of types will be seen to consist rather of clinical groupings; and the associated element, or pathological condition named, does not imply in all instances a causal factor but rather a recognised clinical association. As Collier has written: "The causes of polyneuritis are multitudinous and are, in the majority of the varieties, still undetermined."

Polyneuritis associated with.-

1. Poisons (usually defined aetiologically as

"Toxic" causes).

- (a) Metallic: Lead, arsenic (including organic compounds), bismuth, mercury, copper, zinc, phosphorus, antimony, gold.
 - (b) Organic Extrinsic: Alcohol and its derivatives, chloroform (including chlorodyne), carbon bisulphide, tetrachlorethidene, aniline, dinitrobenzole, trichlorethylphosphate, etc.
 - (c) Exotoxins: Diphtheria, tetanus, botulism.
2. Deprivation and Metabolic Disorders: Diabetes, Beri-beri, Leprosy, Senile degeneration.
 3. Cachetic Conditions: Tuberculosis, Cancer and other Neoplasms, wasting diseases from any cause.
 4. Infections Diseases and Acute Fevers (occurring in train of nearly all): Malaria, Dysentery, Enteric, Influenza, Colitis of all forms.
 5. Gestational or Pregnancy Polyneuritis.
 6. Virus Diseases: only important member is Rabies, in which may occur a rapidly spreading flaccid paralysis.
 7. "Acute Infective" (so-called): febrile and epidemic varieties occurred in soldiers during

the War in 1918, when a filter-passing virus was held to be responsible, but lacked confirmation. Similarly the "Ginger-epidemic" in America, in which the precipitating factor is now held to be trichlorethylphosphate.

8. Associated with Haematoporphrynuria - cause unknown.

9. Associated with Anaemia of all types.

It will readily be appreciated from a study of the above list that there are few of the recognised "Disease groups" with which polyneuritis may not be associated. The frequency with which it may appear as a symptom-complex in diseases of such diverse aetiology rather tempts the supposition that there may be some factor of a toxic, metabolic or other nature common to most of the forms.

I may be inviting criticism by including "Polyneuritis associated with Anaemia" in the classification. No discussion of polyneuritis can be complete without a reference to the peripheral symptoms and signs which are the concomitants of most severe forms of anaemia. Many observers believe that these do not constitute true peripheral neuritis and regard many of the vague

symptoms in the simple anaemias purely as manifestations of bloodlessness or anoxaemia. If the same group of symptoms and signs, but of greater severity, occurs at any time in association with pernicious anaemia, they are diagnosed, usually correctly, as early manifestations of subacute combined degeneration of the spinal cord. Yet in many of these cases there are no signs (when the patient first presents himself) of derangement other than that of the peripheral nerves with or without signs referable to the posterior columns in the spinal cord; signs of lateral column damage may be entirely absent. In other words, the clinical picture as far as the nervous system is concerned, is one of polyneuritis. Whether we are justified in discarding that diagnosis for subacute combined degeneration purely on the discovery of an associated anaemia of the pernicious type is a question which merits very sincere discussion. Whatever view is taken, the fact remains that the clinical picture of a typical polyneuritis and the usual initial stage of subacute combined degeneration of the spinal cord may be indistinguishable, and I shall have the opportunity later of referring to cases of pernicious anaemia which, in the first instance, were diagnosed as polyneuritis before their true significance was realised.

THE PATHOLOGY OF POLYNEURITIS:A comparison of the neurological lesions in some
of the commoner forms.

A review of the literature reveals that the histopathology of the accepted forms of polyneuritis has not, as yet, been comprehensively studied. But no particular form appears to furnish a pathological picture of peripheral nerve changes which may be regarded as specific for the disease with which the polyneuritic manifestations are associated.

Alcoholic Polyneuritis.

Ross and Bury⁴ (1893) in reporting their post-mortem findings in three cases of alcoholic neuritis described early swelling and demyelination of the peripheral nerve fibres, and in one case "some of the ganglion cells of the anterior horns were somewhat destitute of processes". No demyelination of the tracts in the spinal cord was observed. Bury, who concludes the monograph, states - "nerve-fibres may be diseased when no changes can be found in the ganglia in the cord", and emphasizes that changes in the peripheral nerves may lead to lesions in the nerve-centres.

Nonne⁵ (1907) observed in two cases of chronic alcoholism, a loss of myelin in the dorsal columns of the spinal cord and in the periphery of the lateral columns. A third case was found to have similar involvement of both dorsal and lateral columns but little pathological evidence of disease of the peripheral nerves; he named this condition "Myelitis Intrafunicularis". It is significant, however, that this last case was characterised during life by a 'conspicuous anaemia with outspoken cord symptoms' and raises a doubt as to whether the condition was not one of subacute combined degeneration of the spinal cord. Meyer⁶ (1932) drew attention to the association of "Funicular Myelitis" in chronic alcoholism, and concluded that both aetiological and pathologically Beri-beri and Pellagra bore a close relation to this intoxication.

Collier and Adie (quoted by Price, 1934)⁷ describe the peripheral nervous lesion in alcoholism as one of parenchymatous neuritis, the changes being most marked in the small distal branches supplying the skin and muscles, and diminishing in severity as the larger branches are approached. In some cases the spinal cord appears healthy but in the majority of cases modern staining methods reveal changes in the nerve-cells

and degeneration in the tract fibres derived from the posterior roots. In addition, the wasted muscles supplied by the diseased nerves show a reduction in size of the fibres.

Greenfield and Carmichael⁸ (1935) made an interesting histo-pathological study of terminal peripheral nerves from living and post-mortem cases of alcoholic polyneuritis, subacute combined degeneration of the cord and controls. In stained nerve cross-sections, the degree of demyelination was estimated by counts of the number of nerve sheaths remaining, per square millimetre. In normal nerves they numbered 5,000 to 10,000; in the alcoholic and subacute combined degeneration nerves there was a great reduction in number, the counts varying from 2980 to 4,365; the reduction was of the same type but more marked in the alcoholic nerve sheaths. In both instances the great variations in size of the sheaths suggested some separation of the nerve-fibres from the perineurium; it was thought that this might be due either to loss of nerve-tissue or oedema distending the perineurium. Fresh differential counts were therefore made, grouping the myelin sheaths according to size. In normal nerves the sheaths varied from 1 to 10 μ , the majority between 3 and 6 μ .

In subacute combined degeneration nerves there was a general reduction in size, the majority being under 4 u, and very few over 8 u. Similar findings were obtained in the nerves from alcoholic cases. In long sections of nerves from both types of case, there was considerable beading and irregularity of contour of the myelin. (In a case of acute infective polyneuritis, in which death occurred after six weeks, the myelin changes were similar but much more marked and showed gross Wallerian degeneration of individual fibres.)

From these findings Greenfield and Carmichael concluded that the gross abnormalities in the myelin sheaths were evidence of a true degeneration of peripheral nerves. True Wallerian degeneration was not a feature except in the fatal and rapidly progressive cases. The outstanding feature in nerves from both groups of cases was the general impoverishment of myelin; while they were unable to define precisely the nature of the degenerative changes, they considered it unlikely that the axons were affected to any marked degree.

Lead Neuritis and Paralysis.

Collier and Adie (from Price, 1934)⁹ state that

the degenerative changes in nerves in lead neuritis are almost entirely confined to the motor fibres, and are most intense in the intramuscular twigs supplying muscles of the extensor group. Normal and degenerated fibres are found side by side, the former becoming more numerous as the nerve is traced upwards. The lead ascends along the axons and may finally cause the death of the anterior horn cell. Sensory disturbances are slight and may be absent.

Theories of the mechanism of lead paralysis have been evolved which locate the primary lesions in every part of the neuro-muscular apparatus. Friedlander¹⁰ (1879) considered muscular changes in the form of degenerative myositis of first importance, and the involvement of nerves supplying these muscles a secondary manifestation. Kast¹¹ (1880) and Messing¹² (1913) concurred, the latter pointing out that microscopic examination always reveals more marked lesions in the muscle than in any other part of the neuro-muscular apparatus. Most pathologists, however, have considered that the primary lesion of lead paralysis is in the nervous system. Erlenmeyer¹³ (1914), Déjérine¹⁴ (1879), Mosny and Stern¹⁵ (1909), Oeller¹⁶ (1883), Stieglitz¹⁷ (1892), Renaut¹⁸ (1903) and Oppenheim¹⁹ (1885) support

this theory and base their opinion on the distinct degenerative lesions in the anterior horn cells. Lanceraux²⁰ (1862), Westphal²¹ (1874), Déjérine-Klumpke²² (1889), Gombault²³ (1880-81), Charcot²⁴ (1903) and Von Leyden²⁵ (1883) consider changes in the peripheral nerves to be of fundamental importance and describe a distinct Wallerian degeneration in the nerves running to the paralysed muscles. Déjérine-Klumpke (1889) emphasises the fact, which Gombault (1880-81) first observed, that the lesion is distinctly peri-axial.

The more modern conception, however, is that the lesion of lead paralysis is essentially complex. Gordon²⁶ (1905), Wilson²⁷ (1907), Spiller²⁸ (1903) and many others have contributed to this view whilst believing that lead acts upon a particular part of the neurone; according to this view lead affects the part of the neurone which for the time being is rendered most susceptible by its functional condition, i.e., the locus minoris resistentiae - a view pioneered by Raymond²⁹ (1904) and Gordon (1905). More recently Hyslop and Kraus³⁰ (1923) have concluded that the lesion of lead palsy is probably a neuronitis which may be manifested in any part of the neuro-muscular apparatus. In evaluating this observation, however, it must be

pointed out that all examinations were made after death, in many cases the palsy had persisted for several years, and the neuro-muscular system appears to have been focussed upon, to the exclusion of muscle itself.

Whilst von Monakow³¹ (1880) believed that only central lesions could cause paralysis of functionally correlated muscles and explain the symmetrical lesions of lead paralysis, there are other explanations and it is possible that the symmetry of the lesions has been over-emphasized. Some clinical evidence points toward the muscle itself as the site of the action of lead. The susceptibility to muscular fatigue of patients suffering from plumbism has long been recognised, whilst the work of Edinger³² (1908), which recognised the occurrence of paralysis in fatigued muscles was a contribution to the study of lead palsy now generally accepted. In an attempt to explain this observation it has been suggested that since the region with the greatest blood-supply must receive the most lead, the fatigued muscles in which the circulation is increased are exposed to the largest quantity. This, however, does not explain the mechanism of the action of lead. It has been held by many observers that lead has a direct injurious action on both muscle and nerve tissue.

Harnack³³ (1878) believed that lead palsy is due to direct injury of muscle, and Cash³⁴ (1908) showed that after exposure to lead the relaxation time of muscle is prolonged. Dozzi³⁵ (1912) suggested that lead might affect isolated nerve as well as muscle, but his results were obtained by using very concentrated solutions of lead of unknown acidity which contained no other salts. Perhaps the most interesting observations on this problem are those of Aub, Fairhall, Minot and Reznikoff³⁶ (1926), who investigated the action of lead on isolated muscle and nerve, and noted the marked increase in the diffusion of inorganic phosphates from muscle after immersion in lead solution; this diffusion was believed to be due to increase of permeability. After exposure to lead, the muscles were shrunken, of rubbery consistence and lustreless - comparable to the appearance of muscles in rigor. It is significant that rigor is believed to be due to the acid products of fatigue, and ~~that~~ it was found by Aub and associates that the diffusion of phosphates from muscle was increased in acid solutions. It was also found that muscles immersed in lead solution, when made to contract by tetanic stimulation, fatigued more rapidly and more completely than control muscles, and recovered from the

fatigue with greater difficulty.

The direct effect of lead on isolated nerve, and nerve and muscle was investigated. It had previously been found by Reznikoff and Aub that, as judged by muscular response, the conductivity of "leaded" nerve was the same as that of controls. These results were checked by galvanometer methods, using both nerve and muscle as a delicate index of function. The distinct inhibitory action of lead on muscle was confirmed but no deleterious action on nerve was found.

The ample evidence of the linkage between lead palsy and the chemistry of muscular fatigue led to a striking and interesting hypothesis of the mechanism of this action, based on the observation that lead is deposited in bones as insoluble lead phosphate but is mobilized by various changes in metabolism; lead is thought to act in this way because the phosphate is very soluble in acids, especially lactic acid which is liberated in large amounts during muscular activity and fatiguing exercises. When, therefore, lead phosphate circulates through muscle undergoing vigorous exercise, it must be dissolved to a considerable extent by the lactic acid and thus be converted to lead lactate. If such a soluble lead salt comes into contact with a cell,

it can unite with the inorganic phosphate present at the surface and form insoluble lead phosphate and free lactic acid, thus changing the colloidal state and the properties of the cell surface (Aub and Reznikoff,³⁷ 1924).

This work suggests that the physiological lesion of lead palsy is in the muscle itself and that those muscles which are fatigued are most susceptible to lead paralysis. It also suggests that the susceptibility to lead palsy depends on the chemical reactions between lead and the metabolic products formed during muscular activity.

As far as the nervous system is concerned in lead poisoning, there is no doubt that lesions in the peripheral nerves and spinal cord occur. The occurrence of distinct primary lesions other than atrophy in the muscles and simple Wallerian degeneration in the peripheral parts of the nerves, demands some explanation of primary peripheral injury and secondary central degeneration.

Meillière³⁸ (1903) considered that the most vulnerable part of the neurone is affected by lead, and a lesion once formed may spread either centrifugally or centripetally. Although Remak³⁹ (1876) believed the

palsy to be of central origin, he observed that for the most part lesions are present in the muscles and in the peripheral parts of the nerves and that they become less marked centrally.

Legge and Goadby⁴⁰ (1912) emphasized this observation when they noted that the more recent the palsy the more severe are the peripheral lesions, and that as the condition becomes more chronic the central lesions are more marked. The work of Orr and Rows⁴¹ (1914) suggests a mechanism by which the peripheral injury might cause central lesions. Experimenting with tetanus toxin, bacteria and dyes, they demonstrated a lymphogenous drainage from the periphery up the nerve to the cord, and the lesions they described were in the adventitia around the veins and capillaries; and seemed very much like the lesions characteristic of the early stages of various forms of peripheral neuritis.

From these various investigations and observations it is difficult to explain all the phenomena associated with lead paralysis. The action of lead on quiescent and on fatigued muscle appear to be very different. In the light of recent work on the chemistry of muscular activity, it seems probable that the lesion of lead palsy is in the muscle-fibres, and therefore must exert

some influence on the neuro-muscular apparatus. In lead paralysis there seems to be a close chemical and physiological relationship between the action of lead and muscular activity - and therefore of the metabolic changes that occur in muscle - which may have great significance in clinical and therapeutic problems.

The nervous lesion in Beri-beri.

Manson-Bahr⁴² (1935) observes that in beri-beri there is degeneration of the peripheral nerves, more especially of their distal ends and a secondary atrophic degeneration of muscle, including that of the heart, which may be the subject of an acute fatty degeneration like that in diphtheria. Degenerative nerve changes may be detected in the nerve-centres and throughout the implicated neurones as in other forms of peripheral neuritis. Microscopically the nerve trunks show changes from a slight medullary degeneration to complete destruction of nerve fibres (Wallerian degeneration). Regenerative processes occur side by side with degenerative ones. As a rule some fibres in the vagus and sympathetic nerves escape; thus the cardiac branches in the heart muscle and oesophageal twigs are usually unaffected. The ganglion cells in the spinal

cord are only slightly affected. Manson-Bahr comments that "there is very little to be said about the post-mortem appearances in beri-beri which is not covered by the accepted descriptions of the lesions of peripheral neuritis..... the general affection of the whole nervous system involving the central and peripheral structures is identical with that found in diphtheria and alcoholic polyneuritis".

Low and Fairley (quoted by Price, 1934)⁴³ note that in beri-beri the peripheral nerves show a Wallerian degeneration, with possibly an axonal degeneration of the neuron involved. The sheath of Schwann may show multiplication of its nuclei and invasion by leucocytes. The vagus and sympathetic system may present stigmata of degeneration and sometimes the anterior horn cells of the spinal cord and nuclear connections of the vagus in the floor of the fourth ventricle are implicated.

Whilst the observations of the above authors are in general agreement, the literature on the neurological pathology of beri-beri, whether in the human being or in experimental beri-beri in animals and birds, reveals great variety of opinion. Perhaps it would be more correct to say that there has been a diversity of

opinion as to the site of the major nervous lesion capable of correlation with the clinical phenomena in the periphery.

Thus Vedder⁴⁴ (1913) affirmed that beri-beri was characterised by general involvement of the whole nervous system, whilst McCollum and Simmonds⁴⁵ (1918) believed the predominant lesion to be in the motor cells of the spinal cord. Findlay⁴⁶ (1921) based the symptoms and signs on chromatolytic changes in nerve cells. Prickett⁴⁷ (1934) concluded that in B₁ avitaminotic rats the site of the nervous lesion was in the central rather than the peripheral nervous system. Whilst many writers still regard beri-beri as a "peripheral neuritis" and define it as such, others regard the disease as manifesting itself in a failure of growth and development in general, the nervous system merely participating in a general pathological change. It is striking that in so many descriptions of the disease, involvement of the sensory peripheral nerves seems to be a matter of assumption based on the symptoms and signs rather than resting on examination of the nerves themselves. Vedder, Voegtlin and Lake⁴⁸ (1919) contended that the myelin degeneration noted in peripheral nerves in beri-beri bore no relation to the symptoms,

and quoted in support of their contention the frequent immediate recovery after administration of vitamin B₁; they were unable to reconcile this with any profound change in the nervous system.

⁴⁹
Woollard (1927) investigated the pathological changes in the nervous system of rats suffering from experimentally produced beri-beri. He found no degenerative changes in the brain, spinal cord, cranial-nerve nuclei or roots. The vagus nerve was normal, and he could discern no chromatolytic changes in the cells of the central nervous system. He therefore found no evidence to support the theory that beri-beri is a lipoid metabolic disorder.

In the larger nerve-trunks, only an occasional 'doubtful' fibre was seen; as they were examined more distally, pathologically-changed fibres became more frequent. The myelin was agglutinated into globular masses, leaving the axis cylinders uncovered, but the latter were intact despite these medullary changes. These observations are in keeping with those of other observers who, whilst claiming to have found degeneration in larger nerves, are agreed that only a small proportion of fibres were affected.

Woollard comments that if the polyneuritis of

beri-beri commences peripherally, there are four points in the nerve at which degeneration may begin - at the final termination of the nerve, the naked axis cylinder, the smallest intermuscular bundles, or at the entrance to the muscle. The important summary of his findings in the terminal apparatus of both motor and sensory nerves in muscle is as follows:-

1. In some cases there was complete disappearance of the nerve-endings (rare).
2. In some cases the nerve-endings were swollen and had lost their finer differentiation.
3. In some cases the nerve-endings were only slightly changed or not at all.
4. The myelin seemed to suffer more than the axis cylinders; it was of a more fluid consistence as shown by the greater irregularity in outline, and in "spreading" of the sheath even by such slight pressure as the crossing of two nerve-fibres.
5. The changes were more pronounced near the ending of a nerve and became less marked as one approached the larger nerve-bundles. The author believed that in the human being, in chronic cases, the time factor would allow of far-reaching degenerative changes to take place in the nerves.

As there are very few references in the literature of this subject even remotely describing the changes in nerve endings, Woollard's concluding statement is significant: "... in diseases where the symptoms are referable to the periphery, some importance should be

attached to the state of nerve-endings as the neuromuscular apparatus offers a highly differentiated field in which slight morphological changes might be easily observed. I believe they offer a better basis than has hitherto been suggested for the quick recovery that occurs when the animal is given the vitamin. The degree of the changes in the inter-muscular portion of the nerve-fibres and endings as compared with the paucity or absence of changes elsewhere suggest that the disease exerts its effects at this point."

Moore, Plymate and Andrews⁵⁰ (1932) studied the peripheral nerves of rats fed on diets of low vitamin B₁ content. They found no true Wallerian degeneration and did not observe any retardation of myelination; finding no consistent changes in nerves, they did not consider myelin degeneration a valid criterion of vitamin B₁ deficiency. But from their description it would appear that the trunks of nerves were used for the purposes of examination.

Kimura⁵¹ (1919) studied nerve degeneration and regeneration in avian polyneuritis and a human case of beri-beri, and his findings compare favourably with those of Woollard, except that in some nerves he considered the first sign of degeneration was apparent in

the axis cylinder. But the first pathological changes were more frequently found distally in the nerve-fibrils at the neuro-muscular junction. The pernicious effects were quickly counteracted (in the pigeon) by suitable dieting and regenerative processes could be discerned side by side with degenerative. On the subject of nerve-fibre regeneration Kimura believed that his histological studies furnished objective proof of the theory that the new axis cylinder grows in a protoplasmic track while at the same time a simple extension of the old axis cylinder stump, still connected with the nerve-centre, forms the commencing point of the regeneration. The products of degeneration in Kimura's pigeons appeared to be re-absorbed in situ, being suitably 'converted' by the cells of Schwann; while in the human case, white blood cells and mesodermal cells seemed to play a much greater rôle.

Pathological Summary.

It is difficult to draw adequate conclusions from a study of three accepted forms of polyneuritis - those seen in experimental and human beri-beri, alcoholism, and plumbism, and also in the subacute combined degeneration. Very often, from the literature, it is

apparent that the attention of the pathologist has been focussed upon one part of the nervous system to the exclusion of another. Also, many of the observations have been made post-mortem on nervous systems which have been subjected to many years of pathological change, whereas a study of the earliest changes are most desirable. But from a study of the literature quoted, the balance of authoritative opinion definitely favours certain conclusions. Perhaps the chief is that in all these forms of polyneuritis, the pathological change is definitely degenerative in character. Whilst theoretically the peripheral signs could be due to central lesions, there is more evidence that the lesion in most cases has its beginnings at the periphery and the spinal cord changes are secondary. Woollard particularly emphasized the early degenerative changes (demyelination, etc.) which began and were predominant in the nerve-endings and neuro-muscular junction. The nature of the degeneration appears to be of the same type in the polyneurites and in the nerves from cases of subacute combined degeneration of the cord; with a variation in plumbism where the motor-nerve fibres bear the brunt of the changes. Further, in all the forms studied the early degenerative changes were peri-axial

in character and true axonal degeneration was not predominant in early cases. All changes were less marked as one receded from the periphery. If these findings can be accepted, then it is easy to understand the reversible nature of the process, particularly in beri-beri where cure is often of dramatic rapidity. It is also easy to comprehend that the very chronicity of any of these forms of polyneuritis would lead to extensive degeneration eventually affecting the spinal cord and higher centres with concomitant paralysis. (There is no need to invoke any variation in the pathological process to affect this.) This order of procedure is thought to occur in plumbism, alcoholism, beri-beri, and by some observers in subacute combined degeneration of the spinal cord, in untreated or prolonged cases.

The contention of earlier workers that the essential lesion in beri-beri, alcoholism, and plumbism is not a polyneuritis but a degenerative change in the cells of the central nervous system receives little confirmation in the literature. The exact distribution of the degenerative changes in the peripheral nerves and the columns of the spinal cord in the early stages of subacute combined degeneration requires more

adequate investigation. Clinically, many cases exhibit symptoms and signs typical of peripheral neuritis and the initial lesion is allocated to the periphery by some observers. Others maintain that spinal cord lesions, in addition to nerve lesions, are present from the beginning. According to the studies of Greenfield and Carmichael quoted, the changes in peripheral nerves in alcoholic and subacute combined degenerative cases were identical and the only difference was one of degree.

The observation to which I would draw special attention is the potential effect of metabolic and chemical changes in the periphery, and in relation to the neuro-muscular junction - the site at which the early changes in the nerve-endings are first apparent, and where (as was remarked earlier) the nerves are more susceptible to injury on account of their lack of protection. This mechanism was the subject of special investigation in lead paralysis, and Woollard drew particular attention to the importance of the neuro-muscular apparatus as a field for study, observing that the predominance of the early pathological changes suggested that the disease (beri-beri) exerts its major neural effects at this point.

It would therefore appear that metabolic changes in the periphery are of some importance in determining the onset and degree of pathological changes in nerve-endings. In anticipating a future chapter, the important observation may be made in this connection that recent investigation has rendered doubtful the older belief that certain "poisons", such as alcohol, injure peripheral nerves by a direct neurotoxic action. I shall have occasion to emphasize this point with regard to beri-beri where much has been done to elucidate the nature of the bio-chemical lesion in vitamin B₁ deficiency states, and to demonstrate the effect of certain metabolic products on the brain and nervous system.

As regards the polyneuritis associated with other diseased states, I can find no literary evidence to show that the histo-pathology of the peripheral nerves in arsenical polyneuritis differs from that of alcoholic or other common forms of peripheral neuritis, although the intoxication is admittedly different; the clinical nervous manifestations are closely similar.

In diabetic polyneuritis, two distinct findings have been observed (Collier and Adie: from Price, 1934). These consist of degenerative changes in the peripheral

nerves, and, in some cases, degeneration in the fibres of the posterior nerve roots, similar to that found in tabes dorsalis. In diabetes, the severe degree of metabolic changes is fully appreciated.

Making a collective comparison, the pathological similarity of the polyneuritis of beri-beri, diphtheria and alcoholism was noted by Manson-Bahr (1935).⁵² Baelz, Scheube, Pekelharing, and Winkler⁵³ (1882-7) were unable to find any evidence of a specific nature in the nervous lesions of beri-beri, which could not be distinguished from other forms of toxic polyneuritis. Hamilton-Wright (1903)⁵⁴ found changes in both central and peripheral nervous systems like those of alcoholic polyneuritis. L'Hermitte (1916)⁵⁵ describing the nervous lesions in avian polyneuritis, wrote, "la constatation des lésions corticales est un trait de plus qui permet de rapprocher la polynéurite alimentaire aritaminique, le béri-béri expérimental, des polynéurite toxique". Whilst Stitt (1929)⁵⁶ observes: "it is well to remember that beri-beri is but a form of multiple neuritis, which in many cases shows motor and sensory disturbances of the lower portions of the upper and lower extremities; in fact, an extensive epidemic of arsenical neuritis or, to be more exact, a neuritis

in which both alcoholic and arsenical factors were operative, was regarded by eminent authorities as beri-beri."

Polyneuritis: clinical manifestations.

The ensuing description is that of a typical case of alcoholic polyneuritis, in which the phenomena common to most forms of peripheral neuritis are manifest; the description, with slight modifications in onset, rapidity of spread, and distribution applies to other forms such as the arsenical neuritis (and other so-called "toxic" types) and the "dry" type of beri-beri. The early symptoms of many cases of subacute combined degeneration of the spinal cord are also similar.

Symptoms.-

The onset of the polyneuritis is insidious. Premonitory symptoms may be present for weeks or months before actual weakness occurs, such as numbness, tingling, 'pins and needles' sensations in the hands and feet, or cramps in the muscles (usually of the lower limbs). Other sensory phenomena may be present in the early stages - sensations of heat or coldness in the limbs, severe aching or neuralgic pains in the

legs.

These symptoms are often accompanied by painful muscular cramps affecting the calf muscles, usually more severe at night and often causing insomnia.

On examination, some degree of sensory impairment or loss is found affecting the various elements of sensation. Light touch over the skin of the extremities is lost or shows a patchy impairment. Pin-prick causes little pain, or only a blunt sensation is admitted. The discrimination between varying degrees of heat and cold is impaired. The sensory loss is most marked distally in the feet and hands and diminishes towards the knees and elbows - the so-called "glove and stocking" distribution.

Compared with the analgesia or anaesthesia of the skin, there is marked hyperalgesia or hyperaesthesia of the deeper structures. The soles of the feet are tender, the patient often complaining of pain on walking or whilst exerting pressure on the sole of the foot whilst using digging tools. Pressure of the calf-muscles elicits marked tenderness, and this important sign may be present before anaesthesia of the skin is apparent.

Following the disability of these phenomena, some

degree of muscular weakness appears. The weakness may be general, but usually becomes marked in the extensors of the toes, the dorsiflexors of the ankle, and the extensors of the fingers and wrists; sometimes the arms are attacked first.

If the weakness is pronounced, double foot-drop and/or wrist-drop result. The "steppage-gait" of polyneuritis is thus produced, the knees being raised high in walking in order to lift the feet from the ground, and the feet may be "slapped down".

In severe, unchecked cases, the muscular weakness becomes more general, the distal flexor muscles of both extremities, then the proximal muscles, and eventually the muscles of the trunk may be affected. To these disabilities are added muscular wasting and flabbiness, and the muscular imbalance in the limbs leads to contractures in the flexor groups of muscles with resulting deformities.

Trophic and vasomotor disturbances are common and most marked in the extremities; the hands and feet may be white and cold, red or hot, and tend to perspire abnormally. There may be localised oedema of the hands (usually the backs) and feet. The skin tends to become thin, glossy and smooth, and the nails ridged

and brittle.

Reflexes.— In the very earliest "irritable" stages, the deep tendon reflexes may be exaggerated, but by the time the patient comes under observation the converse obtains. The ankle and knee-jerks, the biceps, triceps and supinator jerks diminish and in severe cases disappear. One or two may persist sluggishly or all may be absent. The plantar reflex is often difficult to elicit owing to hyperaesthesia of the sole of the foot, but is flexor. The superficial (cutaneous) reflexes are usually unaltered but may be diminished or absent.

Sphincter control is usually retained so long as the patient is fully conscious.

Sense of position and passive movement in the extremities may be impaired, and in prolonged cases vibration sense may be lost.

In severe cases ataxia may be marked.

Electrical reactions.— There may be a simple diminution of excitability, stronger currents being necessary to elicit muscular contractions. Later true reaction of degeneration may be present in severe prolonged forms.

The end result of prolonged peripheral neuritis which has not responded to treatment is one of flaccid, jerkless paralysis.

BERIBERI and VITAMIN B₁.

Synonyms: Kakke, Barberis, Endemic Multiple Neuritis.

Definition: A disease of dietetic origin, primarily due to deficiency in the diet of the anti-neuritic vitamin (B₁), characterised by multiple peripheral neuritis, and by oedema, effusions and cardiac weakness.

Distribution: Beri-beri occurs principally among the rice-eating populations of Japan, parts of China, India, the Malay Peninsula, Dutch East Indies and the Phillipine Islands. It is also endemic among the inhabitants of Newfoundland, Labrador, etc., who live largely on a diet of white wheaten flour. In Europe and other temperate zones Beri-beri is rare under normal peace conditions, owing largely to the great variety of foodstuffs consumed; but when the diet is considerably restricted through the necessities of war or other periods of stress, outbreaks of the disease are liable to occur. The same may apply to individuals of the poorer classes who live in an otherwise healthy community during normal times.

Beri-beri: introductory note.

Beri-beri is the prototype and the first established of the "diseases of deficiency". It is on the similarity of certain features of this disease and those of other forms of polyneuritis that hypotheses of aetiological and curative significance have recently been put forward. Before identical factors can be established, a study of beri-beri is therefore essential. The following sections do not pretend to furnish a comprehensive survey of all the findings and interesting phenomena associated with beri-beri; they represent but a fragment of the literature on this subject. But while much of the matter quoted may seem irrelevant, an attempt has been made to deal only with aetiological and other factors which were considered pertinent to the subject of polyneuritis in general. The problems of beri-beri must also apply to other forms of polyneuritis if any real degree of correlation exists. Whilst there is much appertaining to both beri-beri and the action and role of vitamin B₁ about which there is as yet no settled agreement, there are at the same time many accepted beliefs. These various factors may now be discussed.

Pathology of Beri-beri:

The pathology of the nervous system, and in particular, the peripheral nerves, has already been described. Low and Fairley⁵⁶ (1934) state that cases of "dry beri-beri" rarely come to autopsy. In the "wet" form of the disease, there is acute congestion of the mucous membrane of the duodenum and lower end of the stomach, sometimes associated with pin-point haemorrhages.

The cardiac muscle may show oedema and degenerative changes, while the naked-eye appearances are those of fatty degeneration associated with dilatation and hypertrophy, especially involving the right side.

Nutmeg-liver, oedema of the soft tissues (anasarca) and effusions into the serous cavities are common.

Adrenal hypertrophy, similar to that described in avian polyneuritis, has been recorded in man.

Manson-Bahr⁵⁷ (1935) observes, "the only lesion which might be considered as specific in beri-beri is the duodenitis which may be present during the first three weeks of the disease, though this is not invariable".

Age incidence.-

Young male adults are most commonly attacked,

also breast-fed infants of mothers suffering from the disease.

Symptoms of Beri-beri.-

There are three characteristic groups of symptoms:-

(1) Multiple peripheral neuritis; (2) oedema and effusions; (3) cardiac weakness. Typically the onset is gradual, being characterised in the early stages by gastro-intestinal symptoms - epigastric discomfort, loss of appetite, nausea and sometimes vomiting and diarrhoea.

Later, the typical symptoms of polyneuritis in the extremities appear, with palpitation, shortness of breath and muscular weakness, the subsequent clinical picture varying according to the predominance of neuritic or cardiac manifestations.

The disease tends to run an afebrile course, except possibly in the early stages, and in epidemic dropsy where a mild degree of fever is the rule. Several different types or forms of beri-beri are described:-

1. Larval, rudimentary or ambulatory cases.
2. Ordinary beri-beri: (a) "wet", (b) "dry".
3. Acute cardiac type.
4. Infantile beri-beri.
5. Epidemic dropsy.

1. Larval or rudimentary beri-beri.

This is characterised by numbness of the legs, with patchy anaesthesia and diminution of knee-jerks, all of which disappear if the condition is recognised and a more varied diet given. Otherwise the condition may remain stationary or progress into the other types. It represents a form of mild chronic beri-beri.

2. Ordinary beri-beri.

(a) "Wet": Following the early gastro-intestinal symptoms, other prodromata such as paraesthesias and heaviness of the limbs are characteristic. The knee and ankle jerks are at first exaggerated and then lost. Tenderness of the calf muscles, blunting of sensation and patches of hyperaesthesia and anaesthesia appear. The patient rapidly develops muscular weakness and is unable to rise from the squatting position.

Varying degrees of oedema become apparent; these often appear first over the tibiae, and later water-logging of the tissues, with effusions into the serous cavities may develop. Shortness of breath, palpitation and tachycardia indicate cardiac involvement, and on examination the heart is dilated, the dilatation particularly involving the right side. Systolic murmurs, associated with equal spacing of the first and

second sounds, are frequently heard; the pulmonary second sound may be accentuated and reduplicated; the pulse is rapid and of low tension, and the blood-pressure low.

Neuritic and paralytic phenomena are not so prominent as the cardiac and oedematous manifestations, but as the oedema clears the muscular wasting becomes more apparent.

Heart failure and sudden death are common.

(b) "Dry": This form is similar to the above except that oedema is absent or slight, the cardiac manifestations are those of irritability, whereas the polyneuritic phenomena with weakness, muscular wasting and paralysis are more prominent. Both motor and sensory nerve-fibres are affected, and the lower extremities are usually first attacked. Paraesthesia and anaesthesia are common but all sensations are affected, these often being first discerned over the tibia. The anaesthesia noted in the lower extremities then becomes apparent about the backs of the hands and finger tips and finger movements are performed clumsily. The hand-grip is noticeably weak. A blunting of sensation is more common than complete anaesthesia. Neuralgic pains, cramps, deep tenderness of the muscles

(especially the calves), associated with absent tendon reflexes are found. Wasting and weakness of the muscles are apparent early and the extensors of the limbs are more affected than the flexors; paralysis may be rapid and widespread and the diaphragm may be affected. Wrist and foot-drop with high-steppage gait may be present, but though the patient may be able to walk unsteadily there is no true ataxia or Rombergism (Low and Fairley). The sphincters are not affected.

Wet beri-beri may develop at any time, just as the dry form may supervene on the wet variety.

(Clinically, the dry form of beri-beri bears a close resemblance to alcoholic polyneuritis, except that the former is more rapid and widespread.)

3. Acute Cardiac beri-beri.

In this form cardiac symptoms may predominate from the onset, or suddenly supervene in either the wet or dry forms. The commonest manifestations present before cardiac decompensation ensues, are precordial pain, epigastric distress, tachycardia, cyanosis, engorgement of cervical veins, pulmonary congestion, hepatic enlargement, oedema of the subcutaneous tissues and serous effusions into the pleura, pericardium or peritoneum. Hoarseness or aphonia resulting from

pressure of the dilated right auricle on the recurrent laryngeal nerve is reported. The diaphragm may be paralysed, and death may supervene in a few hours to a few days.

4. Infantile beri-beri.

This form is commonest in the Phillipine Islands and Japan, where the infant mortality has been very high. The victims are breast-fed infants of mothers affected with latent or clinical beri-beri. The disease occurs in two forms, (a) acute, and (b) chronic. In the former, death may occur rapidly following attacks of severe paroxysmal pain with cyanosis, dyspnoea, tachycardia and muscular rigidity. Extract of rice-polishings and other concentrated forms of the antineuritic vitamin are effective therapeutically, and the infant must be artificially fed. In chronic forms, gastro-intestinal symptoms are most common - anorexia, vomiting, diarrhoea or constipation - associated with wasting and minor degrees of cardiac insufficiency.

5. Epidemic dropsy.

Some authorities class this as a special variety of beri-beri, while others contend it is a distinct disease. It is related to the ingestion of rice,



especially the par-boiled variety, and is characterised by peripheral neuritis and cardiac disturbances. On the other hand the oedema is more generalised, the polyneuritic symptoms less marked, there is usually some degree of pyrexia and an erythematous eruption may involve the extremities. Glaucoma, gastro-intestinal derangement, anaemia, mottling of the skin and a tendency to haemorrhages are other complicating features.

The condition owes its title to the fact that large numbers of rice-eaters are simultaneously affected. Some authorities hold that epidemic dropsy is due to the eating of "degenerated" stored rice, toxic substances being responsible for the disease syndrome. It is usually classified as a form of beri-beri owing to its association with rice and its possessing features common to wet or cardiac beri-beri.

Aetiology of Beri-beri.

Beri-beri is a disease of great antiquity; it was apparently known to ancient Chinese physicians, and the first recorded reference to it is attributed to a medical work by Hwangti, 2697 B.C.

The condition was recognised by the Dutch in their

early intercourse with the East, and was later studied extensively in India. Further writings came from Brazil, and early in the eighteenth century the condition as a multiple neuritis was fully apprehended in Japan.

The association of Beri-beri with a rice dietary was early noted by numerous observers, but was not generally accepted. It is not within the scope of this thesis to quote the host of investigators who have so valuably contributed, step by step, to the elucidation of this disease; the literature is vast and engrossing in its interest, but the following paragraphs summarise the most important steps which have led to our present conceptions.

In 1885 Tahaki⁵⁸ abolished Beri-beri from the Japanese Navy by dietary changes, the chief of which consisted in the partial replacement by barley of the polished rice (the staple article of diet) and additions such as meat and milk. His explanation, based on a nitrogen-deficiency theory was regarded as untenable, however, and in spite of success his views and measures were generally unaccepted.

In 1890, Eijkmann,⁵⁹ an assistant to the Commission appointed by the Dutch Government to investigate the

disease in Java, observed an outbreak amongst his experimental fowls of a disease characterised by polyneuritic signs, and reminiscent of human beri-beri. He was able to trace the outbreak to the giving of boiled rice to the fowls, and noted that the disease disappeared when his new chef refused to supply 'military' rice to them. Eijkmann's pioneer observation on "Avian Polyneuritis" was the first important step towards the elucidation of the disease. But though he was the first to assert the identity of the avian condition with beri-beri, he attributed the fundamental cause, not to a deficiency factor, but to hypothetical noxious substances in the rice carbohydrate, for which the outer layers of rice acted as an antidote.

In 1895, Vorderman⁶⁰ showed experimentally in Java prisons, that the human disease could be produced by the eating of polished rice and arrested or cured by unpolished rice, but his observation attracted little attention.

Grijns⁶¹ (1901) repeated Eijkmann's experiments and proved that a bean (katjangidjo) was both protective and curative for fowls on a polished rice diet. This finding was applied to human beings by Hulshoff Pol⁶² (1901-4) and found to be similarly protective.

Braddon⁶³ in 1907 published an extensive monograph on Beri-beri and showed that the disease definitely followed the exclusive use of polished rice and was prevented by parboiled rice. This was the first accepted proof that the condition was due to rice. His theory was analogous to Eijkmann's, in that he ascribed it to the development of toxins in rice deprived of the pericarp.

Hopkins'⁶⁴ classical experiments in 1906 are now historical, and his formulation of the theory that disease could be due to deficiencies of what he named 'accessory food factors' gave us a new conception of factors which could cause ill-health.

Fraser and Stanton⁶⁵ (1909) showed that beri-beri was a 'disease of deficiency'; they first produced the disease in fowls by feeding them on polished rice after its extraction with alcohol, this being an attempt to remove "toxins". Fowls were also fed on unpolished rice after alcoholic extraction, and again beri-beri resulted. The decisive experiment consisted of feeding fowls on polished rice to which the alcoholic extract of unpolished rice had been added; no beri-beri resulted, nor did it when fowls were fed on undermilled or unpolished rice. They concluded therefore that

"milling" removes some essential substance from the rice, and that beri-beri (or its avian prototype) results from this deficiency.

Funk⁶⁶ (1911) attempted to isolate the "active principle" from rice-polishings, and was the first to apply the term "Vitamines" to the accessory food factors described by Hopkins; he added to our knowledge of Vitamin studies by classifying Pellagra as a deficiency disease in 1912.

The deleterious effects of the milling of rice have since been abundantly proved. A grain of rice consists of an outer husk which is removed in the first part of the process. Beneath the husk are the pericarp or "silver-skin"; the aleurone layer containing the phosphates and fats; the germ or embryo; and lastly the endosperm - the bulk of the grain, containing starch granules. Steam-milling and polishing remove both pericarp and embryo, which contain the vitamin.

The above historical data represent the most important milestones in the classification of Beri-beri as a deficiency disease. Much of the work and most of the conclusions were based upon the assumption that the disease in fowls - avian polyneuritis - and human

beri-beri were analogous. But of recent years the precise relationship of the two diseases has become less certain, as also has the similar condition produced experimentally in animals. There can be little doubt that in all these conditions the deprivation of the antineuritic vitamin is the cardinal factor in their causation. But that it is not the only factor is evidenced by the strange variations in the clinical picture, in the symptomatology and to some extent, the pathology, of these experimentally produced conditions in birds and animals as compared with the disease in man.

The varying results of authoritative observers have consequently led to the formulating of numerous theories in an attempt to explain the aetiological factors in beri-beri. Many of the difficulties have not yet been overcome, and diverse views are still held. These may, with advantage, be examined briefly, as the questions raised with regard to beri-beri are analogous to those which occur in the investigation of other causes of polyneuritis.

Theories as to the causation of Beri-beri.

Many theories have been advanced which attempt to explain the prevalence of beri-beri among rice-eating peoples; since polished rice is known to be poor in many substances - protein, fat, phosphorus, etc. - the disease has been attributed to fat starvation, phosphorus starvation, and low protein content of the diet. An excess of carbohydrate (or a toxin produced as a result of that excess) has been cited as the positive cause.

Beri-beri has been attributed to varying types of infection, to arsenical poisoning and climatic factors; whilst sex, stress and predisposition have been allotted their due aetiological share as contributory factors.

Whilst a deficiency of the antineuritic vitamin (B_1) has been regarded by most as the cardinal factor in the production of the disease, there has been great disagreement as to the nature of its action, and to the part played not only by other members of the vitamin B complex, but by other vitamins as well.

The co-existence of inanition and gastro-intestinal disease are two additional disorders which have added to the controversy on the aetiology of beri-beri.

The Infection theory of beri-beri.

Micro-organisms have long been associated with beri-beri.

Manson⁶⁷ (1901) was convinced, following his Malayan studies of the disease, that the main causal factor was a toxin elaborated by a germ growing outside the body, and was carried by the rice, probably through improper native handling. He also argued that infantile beri-beri was due to the child acquiring a germ disease from the mother.

McCarrison⁶⁸ (1924) in describing two forms of the disease which he had observed in his experimental birds, suggested that certain of his pigeons might be carriers of an invisible virus which exercised a specific effect on epithelial tissues, thus causing a marked difference in the pathological picture.

A reiteration of the infective nature of beri-beri was made in 1923 by Ogata and associates,⁶⁹ and by Nagayo,⁷⁰ and later in 1929 by Matsumara and his collaborators.⁷¹ The last-named group of investigators claimed the isolation from the stools of patients of a *Bacillus Beribericus* and suggested this germ as the causal factor. Two years later, de Araujo⁷² (1931) thoroughly investigated the question in Brazil and

concluded that B. Beribericus was not the cause of the disease in that district; at the same time it is interesting to note that he did not think that the disease was related to a vitamin B deficiency.

Fraga,⁷³ (1923) commenting on Beri-beri in Brazil, believed that an infection was the cause of beri-beri in that country; he based his opinion, not on the finding of any specific organism but on the excellent therapeutic results of neoarsphenamine administered to patients suffering from beri-beri during an epidemic. He was unable to correlate this with a vitamin deficiency. Couto⁷⁴ (1926) also favoured the infection theory, pointing out that Beri-beri occurred only in North Brazil although rice was used in all parts of the country, and that the affected victims not only recovered magically on change of climate but tended to have recurrences of the disease on their return.

Walcott⁷⁵ (1915), however, proved that in the Amazon basin, beri-beri responded to suitable dietetic treatment. Whilst many observers in that country had repeatedly shown that the disease was associated with a rice-free diet, Walcott, by experiments on fowls, was able to show that the common Brazilian food "farina de aqua" was markedly deficient in the antineuritic vitamin.

Much of the tendency to associate beri-beri with an infection has undoubtedly been due to the prevalence of other Tropical infective diseases such as dysentery and malaria, in countries where beri-beri is common. For example, Cannon⁷⁶ (1929) in recording his Hong Kong experiences, states that "the dry and dysenteric beris are really camouflaged forms of malaria, as proved by the invariable findings of the malarial parasite on careful blood examination".

Whilst many observers have not committed themselves to the infectivity theory, there are numerous reports in the literature of the occurrence of beri-beri during or following various tropical diseases. Out of 52 cases reported by Bentley⁷⁷ (1893) in Java, 28 appear to have been the sequel of recurring malaria, dysentery and allied conditions.

Yacoub⁷⁸ (1918) described three cases following relapsing fever, and it is of interest to note that in these cases there was prolonged feeding of condensed milk, a food known to contain very little vitamin B₁.

Walshe⁷⁹ (1918) reported 40 cases of Egyptian beri-beri, 19 of whom had a previous history of malaria.

A recent series of observations by Platt and Lu⁸⁰ (1936), from Shanghai, shows not only the common

occurrence of vitamin A deficiency with beri-beri but records a number of cases from their series showing marked manifestations of both vitamin A and B₁ deficiency occurring in the course of other diseases. These include broncho- and lobar- pneumonia, pulmonary tuberculosis, typhoid fever, bacillary dysentery, meningococcal meningitis, tuberculous meningitis, Ningpo varnish poisoning, cardiac failure and malaria. These observers are careful to point out that whilst recognising the past tendency to regard beri-beri, in many instances, as secondary to various diseases, "careful inquiry in such cases will often be rewarded by a history of minor manifestations of beri-beri preceding the onset of the supposedly primary complaint". It is therefore not surprising that the frequent occurrence of beri-beri coincident with, or as a sequel to, tropical fevers, ankylostomiasis, prolonged diarrhoea from any cause, and the diseases enumerated above, should have led clinicians to adopt the view that beri-beri is primarily an infection rather than a deficiency disease.

The Intoxication Theory of beri-beri.

Probably the oldest hypothesis of the origin of

beri-beri is that the disease is the expression of an intoxication. A survey of the literature reveals the great diversity of opinion as to the fundamental factor in the intoxication. Eijkmann's original interpretation of his observation that a diet over-rich in starch produced an unknown noxia in the bowel has been referred to. Braddon (1907) after an intensive investigation of beri-beri, came to an analogous conclusion.

Carbon dioxide and oxalic acid have been cited in this connection, whilst Ross⁸¹ (1901) believed that beri-beri was due to arsenical poisoning.

The frequency with which the disease occurred in rice-eating people in the East naturally caused suspicion to fall on factors in the foodstuffs concerned. Thus, organic substances such as "ptomaines" were suggested, and other purely hypothetical poisons believed to be present in common foods such as rice and fish - the food most commonly used to supplement polished rice in the Orient, were cited.

The majority of these hypotheses were formulated before the significance of accessory food factors and deficiency diseases had been discovered. It was but natural that they should compare beri-beri with other known forms of "toxic" polyneuritis - alcoholic,

arsenical and diphtheritic; presented with a symptomatology and morbid anatomy similar to those of an intoxication, they were unable to exclude the probability that beri-beri was due to a positive cause of toxic nature.

Even after the increasing recognition of the importance of vitamin deficiencies, many investigators still claimed that an intoxication was the primary factor. Kohlbrügge⁸² (1911) definitely associated beri-beri and Barlow's disease and tended to connect them both with unbalanced diets too rich in starch; he contended that such diets favoured the growth of fermentative bacteria which formed acids in the bowel, depressing or extinguishing the normal flora; hence he designated them "fermentation diseases".

Toxic factors have been stressed as causative agents in the writings of Mott and Halliburton⁸³ (1899), of Stanley⁸⁴ (1903), of Hamilton Wright⁸⁵ (1905), of Braddon⁸⁶ (1905-1907) and Walshe⁸⁷ (1917-18; 1920) among others. That wheat embryo was thought to contain a toxic factor which could be extracted by ether was suggested by McCallum, Simmonds and Pitz⁸⁸ (1916); and Williams⁸⁹ (1927) described a toxic condition in pigeons fed exclusively on rice-bran or rice-polishings -

substances rich in vitamin B₁; he suggested that toxaemias play a definite role in determining the symptoms of deficiency diseases, and that foodstuffs, though not toxic in the ordinary sense, might become so when other dietary defects remained uncorrected.

The numerous attempts to prove the existence of toxins have led eventually to a newer conception which attempts to harmonize the intoxication theory with the vitamin-deficiency hypothesis, and more intense investigation has recently been carried out on the various metabolic derangements that may occur in vitamin B₁ deficiency, with the production of certain metabolites believed by many to act as toxic agents. This hypothesis implies that the metabolites are the expression of a prolonged shortage of vitamin B₁. As this question is becoming more and more important, it may be deemed advisable to summarise briefly the conclusions reached in this connection.

The Relation of Vitamin B₁ to Metabolism.

It has been pointed out that emphasis has been laid from the time of Eijkmann's first observations on the importance of metabolism in general, and carbohydrate metabolism in particular, in the aetiology of beri-beri.

Much of the evidence is conflicting, since it was written before the significance of the many factors in the vitamin B complex was appreciated. In addition, the imperfectly understood part played by other vitamins, hormones, minerals, and concomitant disease processes, as contributory factors to the varying clinical picture, have added to the confusion. Attention, therefore, has been divided between the significance of the anti-neuritic factor for metabolic processes as a whole, and its specific relationship to any particular group of food material. Much re-interpretation of earlier clinical, pathological and laboratory findings is required, since many of these pertained to the Vitamin B complex as a whole. The isolation of the B₁ factor from the vitamin B complex has considerably assisted the course of the investigations.

Temperature.

Many investigators have recorded a fall in body temperature in animals and birds deprived of the anti-neuritic vitamin, up to a complete loss of temperature regulation. This has been stressed by Eijkmann⁹⁰ (1897), Drummond⁹¹ (1918), Novaro⁹² (1920), McCarrison⁹³ (1921), Drummond and Marrison⁹⁴ (1926) et al. All affirmed that administration of the vitamin was followed

by a return of the temperature balance, often of a dramatic rapidity.

Protein intake.

There is little available data as to any authentic relationship between protein metabolism and vitamin B₁. Funk⁹⁵ (1914) observed that the rapidity of onset of polyneuritis was not affected by increasing the amount of protein in the diet. On the other hand, Hartwell⁹⁶ (1922) recorded that the amount of vitamin B required by the rat in order to ensure efficient lactation was proportional to the protein content of the diet. Drummond, Crowden and Hill⁹⁷ (1922) and Reader and Drummond⁹⁸ (1926) observed that there must be a definite relationship between the protein intake and the amount of vitamin B to ensure normal growth.

Tscherkes⁹⁹ (1926) believed that vitamin B bore a definite relation both to carbohydrate and protein metabolism.

Doubt as to the exact significance of the anti-neuritic vitamin in protein metabolism was expressed by Hassan and Drummond¹⁰⁰ (1927), who showed that the vitamin associated with protein metabolism was stable to treatment with hot alkali - a chemical indication that vitamin B₁ was not the factor concerned, although

vitamin B₂ may be.

Platt and Lu¹⁰¹ (1936), in discussing the characteristic effects of vitamin B₁ deficiency and changes in metabolism wrote: "It is believed, however, that protein and fats also share in this effect since the vitamin B₁ requirements of the body are determined by the total caloric intake irrespective of the nature of the diet."

The exact relationship of the antineuritic vitamin to protein metabolism is by no means a settled question, though hitherto there have been few findings to indicate that this aspect of the problem is of major importance. The association of the vitamin B requirement of the body and carbohydrate metabolism, however, has assumed an importance of some magnitude in recent years.

Carbohydrate Metabolism.

No useful purpose would be served by reviewing all the early literature on this problem. It is sufficient to say that since the study of beri-beri first caught the imagination of investigators, the existence of some relationship between carbohydrate intake and the occurrence of beri-beri has been repeatedly stressed. The literature teems with references to this subject

and a great variety of interpretations has been advanced to explain the relationship. The following may be cited as important authoritative opinions which have led, step by step, to many of our present conceptions.

Funk¹⁰² (1914) observed that the symptoms of beri-beri did not appear in fasting birds but that an increase in the amount of food ingested, especially of carbohydrate, hastened the onset of polyneuritis. He advanced the theory that the time of onset of the disease in individuals was to a large extent dependent on the amount of vitamin B stored in the body from the previous diet, and the nature and amount of food ingested during the avitaminous period. Braddon and Cooper¹⁰³ (1914) confirmed Funk's observations with respect to carbohydrate intake but did not agree with his theory.

Previous to these observations, Abderhalden and Lampne¹⁰⁴ (1913) also noted that pigeons starved to death failed to develop polyneuritis, and a similar finding was made by Chamberlain and Vedder¹⁰⁵ (1911), who considered that in most cases the birds died before the polyneuritis had had time to develop. In support of this contention, Chamberlain, Bloomberg and

Kilbourne¹⁰⁶ (1911) and Marrian, Baker, Drummond and Woollard¹⁰⁷ (1927) claimed that in a few of their experimental birds symptoms of polyneuritis had developed before they succumbed.

Walshe¹⁰⁸ (1918) claimed that two factors are concerned in the production of Beri-beri: the absence of the antineuritic vitamin and the use of certain foods which are the direct and immediate cause of the disease; that, in the absence of the vitamin, carbohydrates undergo an aberrant hydrolysis with the production of toxic by- and end-products, thus producing beri-beri. In Walshe's opinion, the disease was an intoxication and he suggested the relationship of the vitamin to an enzyme concerned with the hydrolysis of carbohydrates.

Dutcher¹⁰⁹ (1918) considered that the condition produced by withholding the antineuritic vitamin was due to an overloading of the oxidative mechanism of the body rather than to any specific relation between the metabolism of carbohydrates and the vitamin, the latter being used up in the process. In 1920, the same observer found that in specific fasting for vitamin B₁ the accumulation of incompletely metabolised products may affect the nervous system and account for the loss

of function; further, he contended that the vitamin functions as a metabolic stimulant since the body temperature falls during the development of avian polyneuritis and rises after administering the vitamins; this was correlated with observations on the catalase content of the tissues which was decreased to 56% of the normal and returned to normal after giving the antineuritic vitamin. Dutcher concluded that such a depression of oxidation resulted in the accumulation of toxic metabolic products which affected the nervous system.

Further direct evidence bearing on this problem came from Collazo¹¹⁰ (1923) who found that after introducing considerable amounts of carbohydrate into the crops of normal and B₁-avitaminous birds, death invariably occurred in the latter though not in the former; and that of the carbohydrates used, monosaccharides produced the most toxic effect, starch the least, while disaccharides occupied an intermediate position. He claimed, therefore, that as a result of vitamin B₁ deprivation, carbohydrate metabolism was deranged, with the production of toxic substances. An important additional observation followed when it was shown (Rubino and Collazo,¹¹¹ 1928) that the

carbohydrate thus introduced was actually absorbed, but that the liver was unable to store it.

Following his extensive studies on avian polyneuritis, McCarrison¹¹² (1928) came to the conclusion that Beriberi Columbarum was something more than a specific dietary deficiency, and considered that in addition to a vitamin B₁ deficiency there was a toxic factor dependent not so much on an absolute lack of the anti-neuritic vitamin in the diet as on a relative insufficiency of it. He found no evidence to support the theory that any toxin was produced from rice as a result of bacterial action, but regarded the noxious substance as a product of deranged metabolism, analogous to the ketone bodies in diabetes mellitus. Thus he concludes: "The diversity of symptoms and pathological changes resulting from vitamin deficiency will be determined by the varying biochemical response of different individuals to this influence, and by the extent to which the specific excitant of true beri-beri is produced within their bodies."

The Biochemical Lesion in Vitamin B₁ Deficiency.

Research studies of metabolic changes have irresistibly led to a more intense investigation of biochemical abnormalities, particularly with regard to certain oxidase systems in relation to vitamin B₁ deficiency. Dutcher's observation on the catalase content of the tissues has already been referred to, whilst Findlay¹¹³ (1921) noted that the glyoxalase content of the liver was decreased in the absence of vitamin B, but increased again when it was administered. Whether any diminution in the oxidative capacity of the tissues is specific for a vitamin B₁ deficiency has been the subject of much controversy. Opinion has been divided as to the extent of the specific biochemical lesion in the glucose-lactate system and the relation of this to the vitamin deficiency, per se, and the accompanying inanition. These discussions have centred around such biochemical problems as basal metabolism, respiratory exchange, oxygen uptake of avitaminotic tissues, and the effects of various substrates used in the experiments. The conclusions are important, and certain of them are now generally agreed upon. That vitamin B₁ and carbohydrate metabolism are definitely and significantly related is an established

fact, and the following represent some of the important citations in the chain of evidence.

Roche¹¹⁴ (1931) confirmed the findings of previous observers as to the disturbance of carbohydrate metabolism in experimental vitamin B deficiency, and noted an increase in the ratio C/N of the deproteinized blood filtrates, caused partly by hyperglycemia and partly by the accumulation of intermediate products of carbohydrate metabolism.

Kinnersly and Peters¹¹⁵ (1929, 1930-1) found that in the terminal stages of vitamin B₁ deficiency, the brains of pigeons showed an increased lactic acid content; this appeared to be localised in the region of the hind-brain, and differed in this respect from the condition after exercise when the lactic acid content was general. Fisher¹¹⁶ (1931) and Landsgaard¹¹⁷ (1930) also showed the lactic acid content to be raised in the heart, liver and muscles of polyneuritic pigeons, and that it returned more slowly after exercise to normal. Birds cured with Marmite (a food very rich in vitamin B₁) behaved normally. Similar investigations were made in human beings suffering from beri-beri by Inawashiro and Hayasaka¹¹⁸ (1928, 1929-30). They found that the lactic acid content of the blood was

higher than normal and took longer to return to the initial level after exercise; from this they concluded that the resynthesis of lactic acid in the muscles was retarded in beri-beri.

Biochemical investigation upon oxygen uptake and tissue respiration in liver, brain, muscle and other tissues was carried out either in the presence or absence of various substances added as substrates. Thus Abderhalden et al¹¹⁹ (1920-2) and W. R. Hess¹²⁰ (1921) claimed that there was a specific change either of actual oxygen uptake or of dye reduction in the presence or absence of succinate (used as substrate); Roche¹²¹ (1925) reached a similar conclusion. Kollath¹²² (1929) compared the effects in normal, starving and polyneuritic pigeons, and concluded that in polyneuritis there was a demonstrable change in the oxidation-reduction potential of certain organs, associated with changes in cell permeability. That differences in the oxygen-uptake of pigeons' tissues can be shown in the absence of added substrate was reiterated by Abderhalden and Vlassipoulos¹²³ (1930). These observers, and later Gavrilesco and Peters¹²⁴ (1931) found a very slight and insignificant reduction in oxygen uptake by pigeon's brain without added substrates for

avitaminous compared with normal birds. With added glucose (or more readily with lactate), marked decreases in oxygen-uptake of 20 per cent. and 40 per cent. respectively were found. When succinate was added as substrate to the tissues of avitaminous birds, there was no departure from normal. Great significance was attached to these experiments of Gavrilesco and Peters, in that when vitamin B₁ concentrates were added in amounts of 1 γ (.001 mg.) or less per 100 mg. tissue, the oxygen uptake in the presence of glucose or lactate was largely restored; but the same vitamin concentrates had little influence on normal brain with added lactate, or on avitaminous brain with added succinate. Two inferences were drawn from these experiments: that the active agent in restoring oxygen uptake (in the concentrates) was vitamin B₁; and that the diminished oxygen uptake in the second group of experiments was not solely due to diminished amounts of tissue substrates. At this time, therefore, the conclusion was reached that a deprivation of vitamin B₁ superimposed specific biochemical lesions in the "Glucose-lactate system" upon any changes that might be due to the accompanying inanition.

To the above work, much of value has been added

during the last few years, and the results of Peters' investigations¹²⁵ (1936) and conclusions furnish a valuable resumé of the work done in this field. There has been positive evidence from many investigators (Clift and Cook¹²⁶, 1932; Thompson,¹²⁷ 1934; Johnson, Meiklejohn, Passmore and Thompson,¹²⁸ 1935; Thompson and Peters,¹²⁹ 1934; Thompson and Johnson,¹³⁰ 1935; et al) of the accumulation in the blood and tissues in B₁-avitaminosis of certain substances to which the term "Bisulphite binding substances" (B.B.S.) has been given. Increased amounts of lactic acid have been shown to occur in the blood of beri-beri patients; methyl glyoxal has been found in the urine and cerebrospinal fluid of infants suffering from a toxæmia responding to treatment with vitamin B₁ (Geiger and Rosenberg,¹³¹ 1933). Methyl glyoxal or a similar substance is also believed to be secreted in the milk and excreted in the urine of B-avitaminotic mothers and has been identified in the blood of infants suffering from beri-beri (Platt and Lu,¹³² 1936). Another, possibly more important member of this group of bisulphite binding substances - pyruvic acid - has been demonstrated by numerous investigators in the blood and tissues of B₁ avitaminotic animals and birds, and in

the blood, cerebro-spinal fluid and urine of beri-beri patients. It seems highly probable that there are many other as yet unidentified substances comprising the "B.B.S." group, the significance of which in B vitamin deficiency states has not yet been fully appreciated; that is, in cases of acute or fulminating beri-beri, when the amounts of known bisulphite-binding substances such as pyruvic acid and methyl glyoxal have been estimated separately, and the total B.B.S. collectively, there is a definite percentage of the latter still unaccounted for. Formaldehyde and acetaldehyde are two substances suggested by Platt and Lu (1936) which might conceivably belong to this group, and which might tend to accumulate in abnormal amounts in severe states of vitamin B₁ deficiency. Much interest has centred round the question as to whether substances such as pyruvic acid are normal or abnormal metabolites, occurring during the course of normal carbohydrate metabolism or appearing in demonstrable amount in blood and tissue only when a pronounced biochemical lesion has occurred. Recent research has, to some extent, clarified matters, and has shed new light on the role of vitamin B₁ in carbohydrate metabolism.

Thompson and Johnson¹³³ (1935) showed that there

was a marked rise in the amount of pyruvic acid in the blood of a pigeon deprived of vitamin B₁, and a decrease when the vitamin had been restored; in one bird the figures were: Normal blood, 3.96 mgs. per 100 grams blood; during B₁ avitaminosis, 11.31 mgs. per cent.; after "cure", 5.29 mgs. per cent. Analogous readings were found in rats, the normal level being about 4.22 mgs. per 100 grams blood, and 9.39 mgs. in B₁ avitaminosis. Peters¹³⁴ (1934) was unable to demonstrate the presence of pyruvate, in vitro, in appreciable amount in the normal pigeon's brain; but he showed that pyruvate was formed with a B₁ avitaminotic brain in the absence, but not in the presence of, the vitamin; that the addition of vitamin B₁ caused the disappearance of added pyruvate; and that there was no demonstrable amount of pyruvate present in the B₁ avitaminotic pigeon's brain at death. Peters concluded from these experiments that pyruvate was never present in appreciable amount in the normally respiring pigeon's brain; that it was formed from lactate in the B₁ avitaminotic brain in the absence, but not in the presence of vitamin B₁; and that the addition of the vitamin was responsible for the disappearance of the added pyruvate.

There was, obviously, from these investigations, some justification for associating the cerebral signs, such as opisthotonos, and emprosthotonus (which may occur acutely in pigeons deprived of vitamin B₁) and the presence of large amounts of pyruvate in the brain tissue. Secondly, the dramatic rapidity with which the pathological signs disappeared after administering the antineuritic vitamin admitted of some association with the simultaneous reduction or disappearance of pyruvate from the brain-tissue.

Further interest attaches to the observations of Johnson, Meiklejohn, Passmore and Thompson (1935) who were unable to demonstrate the presence of pyruvic acid itself in human blood in "ordinary diseased conditions". On the other hand, Platt and Lu (1935) found not only increased bisulphite binding substances in acute beri-beri, but demonstrable amounts (often large) of pyruvate in the blood and cerebro-spinal fluid of these patients.

The results of a recent series of experiments by Peters¹³⁵ (1936) on the biochemical lesions of vitamin B₁ in the pigeon may, with advantage, be quoted. (The investigations were carried out on brain tissue in vitro, using various substrates and concentrates of vitamin B₁;

the method and technique are fully described in Peters' original work.)

1. There was reduced tissue respiration (oxygen uptake) in the brain of the B₁ avitaminotic pigeon.
2. The addition of vitamin B₁ to such tissue largely restored the oxygen uptake in vitro; moreover there was a regular relation between the effect of the vitamin on oxygen uptake and the amount of vitamin added up to a certain maximal amount, e.g., with the amount of tissue and solution used as little as 1/10,000 mg. vitamin had a perceptible effect, and 1/500 mg. was maximal.
3. This action was so regular that it could be used as a test of the vitamin.
4. The lowered oxygen uptake observed in B₁ avitaminotic brain in glucose, lactate and pyruvate media was due to lack of vitamin B₁ in the tissue. In strong contrast to the results with glucose, lactate and pyruvate, no difference at all was found between the behaviour of normal and B₁ avitaminous brain tissues when succinate was used as a substrate. The importance of this lies in the fact that

succinate does not belong to the carbohydrate intermediary series of substances. It could be definitely concluded that a vitamin B₁ deficiency affects the sugar metabolism at some point related to the 3-carbon stage.

Peters therefore contended that these facts gave substance to two old theories of the action of vitamin B₁: (a) that it is concerned with carbohydrate metabolism, and (b) that it is concerned with tissue-respiration - both views being correct. Peters stressed the importance of the demonstration of pyruvic acid as a normal carbohydrate metabolite and of its disappearance on the addition of vitamin B₁. Peters observed that the experiments proved that the vitamin was not a lactate oxidase co-enzyme but "a catalyst needed for the oxidative removal of one of the lower degradation products of carbohydrate metabolism". He suggests two possible "schemes" for its action:-

- (a) Vitamin B₁, in the presence of pyrophosphate leads to the formation of some substance (unknown) which interacts with the lactate-pyruvate system and leads to increased oxygen uptake;

or (more probably) .

- (b) Lactate (+pyrophosphate) → pyruvate, this being directly oxidised in the presence of vitamin B₁.

The association of these findings with the clinical and pathological signs in the pigeon suggested two hypotheses. The signs produced by the nervous lesions could be the result of the accumulation of lactate and pyruvate (methyl glyoxal was not found in the pigeon's brain tissue) - these substances exerting a toxic influence; or the nervous phenomena could be interpreted purely as the results of a Deficiency, without invoking any toxic factors. Peters boldly eliminates such hypothetical factors as intestinal toxaemia, and doubts whether the toxicity view can be justifiably supported; the earlier discoveries of lactate accumulations had inclined him towards the toxicity theory but attempts to induce symptoms by lactate injections had been futile (Birch and Harris,¹³⁶ 1934); secondly, the amount of pyruvate in the blood was very small and there was no evidence of increased pyruvate in the pigeon's brain at death. There was, therefore, no experimental support for the idea of toxicity by the accumulation of normal metabolites in brain cells.

Asserting his belief in the "Deficiency" hypothesis, Peters writes: "The absence of an important factor in the development of energy from carbohydrates would be sufficient to stop the normal functioning of some groups

of nerve-cells. Those which normally have most work to do might be expected to run out sooner of their supply of the catalyst vitamin B₁ than others, i.e., interrupt the normal metabolism of glucose at any stage and brain-cells do not function properly." This view of Peters receives some support from his investigations in 1929, when he showed that similar nervous symptoms were developed in the pigeon (*emprosthonus*, etc.) by asphyxia, insulin overdosage, cyanide poisoning and anaesthesia such as chloroform; these were believed to cause interference at some stage in sugar metabolism. Questal and colleagues¹³⁷ (1936) showed that narcotics influenced the lactate oxidations far more than the succinate. These instances are cited by Peters to support his view that failure of function of a nerve-cell will take place if the metabolism of that cell is interfered with, and there is no necessity to invoke the idea of a toxic agent, as such, to explain the abrogation of function.

Peters, however, finds difficulty in associating satisfactorily the biochemical lesion described above and the more prolonged symptoms in polyneuritic birds in which the acute cerebral signs are not predominant, and in which the response to vitamin B₁ is not so

dramatic. He suggests that there must be some more extensive cell change to explain the different clinical picture.

Nevertheless, though these studies are, at the moment, fragmentary and defective in several important respects, they have restored some vestige of order out of chaos. The findings of greatest import can be summarised thus:

1. Vitamin B₁ is a catalyst needed for the removal of some of the lower degradation products of carbohydrate metabolism.
2. In both experimental B₁ avitaminotic states and in human beri-beri, these products - of which Lactic acid, Pyruvic acid and Methyl glyoxal have been identified - tend to accumulate in amount.
3. The administration of vitamin B₁ tends to their reduction or disappearance by oxidation.
4. Vitamin B₁ is thereby shown to be actively concerned in tissue respiration, and in carbohydrate metabolism.

The Bisulphite Binding Substances (B.B.S.)
in Beri-beri.

From the foregoing description of the biochemical lesion in B₁ avitaminosis, one may advance the criticism that most of the investigations were carried out experimentally in birds and rats; that the cerebral symptomatology in the pigeon (opisthotonus or emprothotonus, etc., marking the acute form of the avitaminotic state) is obviously different from the polyneuritic manifestation of human beri-beri; and that Peters' experiments were performed on brain tissue, in vitro. Before assessing the value of these biochemical findings as an index of B₁ avitaminosis, one is justified in seeking practical application of their significance in the naturally-occurring form of beri-beri or other states of B₁ avitaminosis in man.

It is interesting to find, therefore, that a large series of cases of beri-beri was specifically studied with this end in view by Platt and Lu in Shanghai¹³⁸ (1936). The cases included all degrees of severity - acute or fulminating, subacute, "wet", "dry" or atrophic, cases in which there were signs of a co-existing vitamin A deficiency, and others complicated by diseases

such as pulmonary tuberculosis, typhoid, malaria, etc. The chemical investigations included the estimation of the total amounts of bisulphite binding substances (B.B.S.), pyruvic acid and methyl glyoxal in blood, cerebro-spinal fluid and urine. The findings are as follows:-

1. In a series of normal, healthy Chinese students varying in age from 15 to 34 years, the B.B.S. values mg./100 grm. varied from 2.22 to 4.82 with a mean value of 3.27 mg. (expressed as pyruvic acid in 100 grm. blood).

(This may be compared with the figures of Johnson and associates (1935), who obtained an average value for bisulphite binding substances in normal human blood in this country of 2.81 mg. per 100 grm.)

2. In fulminating beri-beri gross changes in the B.B.S. values were obtained, increases up to 16.1 mg./100 grm. in blood, 10.1 mg./100 grm. in cerebro-spinal fluid, and 81.4 mg./100 grm. in the urine, being found. These increases were due mainly to pyruvic acid (confirmed by isolation from the blood of the 2,4 dinitrophenylhydrazone of pyruvic acid

in several cases), but the authors are careful to point out "the small part played by pyruvic acid in some cases in the increase of B.B.S. - the question immediately arising as to the nature of the other substances contributing to this increase". In some cases methyl glyoxal was found, and with appreciable amounts of this substance the authors were led to suspect a more profound toxaemia.

3. In the dry atrophic form of beri-beri, normal B.B.S. values were obtained.
4. In 'ordinary' and 'sub-acute' beri-beri patients, the amount of B.B.S. in the blood was not significantly different from the amounts found in normal subjects.
5. There was a marked and often dramatic fall in the B.B.S. values following administration of vitamin B₁ concentrates, in many cases, correlated by definite clinical improvement; e.g., one patient with B.B.S. of 5.39 mg./100 gm. (blood) was given 2000 Peters' pigeon units intravenously; blood taken one hour later showed a B.B.S. value of 3.88 mg./100 gm., the pulse had fallen from 110 to 80, all symptoms were relieved; twelve

hours later the pulse was 65, there was no oedema and the tendon reflexes, elicited only with difficulty on admission, were now brisk.

6. The amount of B.B.S. present in the blood appeared to follow the degree of vitamin B₁ deficiency as determined by clinical criteria; this seemed to hold good for comparison of different cases as well as for the course of remission in any one case.
7. A means of biochemical standardization and control of treatment by vitamin B₁ concentrates was afforded. But there were indications that much larger doses of vitamin B₁ might be needed than those used hitherto.
8. There could be little doubt of the close correlation between the clinical manifestations of vitamin B₁ deficiency and the accumulation of bisulphite binding substances in the blood, and of these, pyruvic acid or some easily hydrolysed compound such as phospho-pyruvic acid, was probably most important. At the same time the study was far from being complete, and the question of the specificity of the B.B.S. determination as an index

of vitamin B₁ deficiency required further investigation.

The opinions of Platt and Lu on the relationship of the accumulated chemical substances in the blood to the clinical manifestations, are of great interest and may be contrasted with the opinion of Peters, in that they are based on studies of a naturally occurring B₁ avitaminotic state in man, as compared with that experimentally produced in the pigeon by the latter. The observations of Platt and Lu, founded on an intensive study of a very large series of cases of beri-beri may, with advantage, be quoted. "It may be the substances (B.B.S.) are not themselves toxic, but that they stand in much the same relationship that urea does to the phenomena of uraemia. Indeed, we know that in some of our severer cases, there is a very high level of non-protein nitrogenous substances in the blood. There may also be an increase in the 'reducing sugar' in the blood, and we intend to examine the nature of this 'sugar' more in detail before making further statements on this point. There is also increased excretion of Creatine in the urine of the more severe cases of beri-beri, an observation which, taken together with the localization of pain, cramps and

fatigue phenomena in the muscles, and the question of the site of production of the pyruvic acid, directs attention to a re-examination of the relationship of vitamin B₁ to metabolism in muscle. The interplay of a number of deficiencies in the diet is believed to be of fundamental importance in determining the features of 'ordinary' beri-beri.

Mainly from clinical considerations it is held that the degree of vitamin A deficiency materially modifies the course of the disease; whilst the occasional occurrence of true pellagra, together with certain changes in the mouth and in the distribution of pigmentation on the face, hands and feet has led us to suspect the widespread prevalence in the same patients of insufficiency of the vitamin B₂ complex.

That the localization of the lesion in a limb in vitamin B₁ deficiency is often determined by the amount of muscular activity has already been indicated (Platt and Gin,¹³⁹ 1934). The accumulation of metabolites in the affected part will undoubtedly contribute to the manifestations of vitamin B₁ deficiency, but the extent to which structures are attacked may well be determined by the degree of hypovitaminosis A pre-existing. If this proves to be the case, then the form in which, for example, damage to nervous tissue is

manifested, may be materially modified." Platt and Lu illustrate this point by contrasting the findings in patients suffering mainly from vitamin B₁ deficiency in whom the peripheral neuritis was completely cured after a few days, with those in subjects who conformed to the dry, atrophic type of beri-beri, in which these authors (mainly on clinical grounds, associated xerosis of skin and hair, ridging of nails, follicular keratosis, etc.) believe there to be a concomitant deficiency of vitamin A. In these "dry" beri-beri cases the values for bisulphite binding substances were found to be within normal limits.

Hyperglycaemia. With reference to the 'suspicion' of Platt and Lu, quoted above, that there appears to be an increase in the amount of reducing sugar in the blood, further references to the literature bearing on the possible association of B₁ avitaminosis and hyperglycaemia are desirable. Funk and Schönborn¹⁴⁰ (1914) recorded that pigeons fed on a diet of polished rice developed hyperglycaemia with a corresponding diminution in the glycogen content of the liver. This hyperglycaemia finding has been confirmed by many other investigators for the pigeon, and for the rat by Lepkorsky, Wood and Evans¹⁴¹ (1930) and by Eggleton and

Gross¹⁴² (1925). A similar condition, however, was observed by Marrian, Baker, Drummond and Woollard¹⁴³ (1927) in pigeons during starvation, and believed by them to be due to the inanition.

In their experiments on B₁ avitaminosis, Gulland and Peters¹⁴⁴ (1930) observed no change in the concentration of non-glucose reducing substances in the blood, and Eggleton and Gross (1925) found no change in the rate of absorption of glucose.

Human Beri-beri and experimental Vitamin B₁

deficiency: are they the same?

Before discussing this question, it is pertinent to refer once again to the clinical and pathological variations obtained experimentally at various times in the same species of animal or bird by withholding the antineuritic vitamin. One outstanding example may be quoted. McCarrison¹⁴⁵ ((1928) in an extensive study of Avian Polyneuritis was able to distinguish two types of the disease. He named them Polyneuritis Columbarum (analogous to the condition described by Eijkmann and others) and Beri-beri Columbarum. Polyneuritis Columbarum is characterised by anorexia, asthenia,

intestinal fluxes and symptoms attributable to derangements of the nervous system - peripheral neuritis, opisthotonos and emprosthotonos. Pathologically the condition shows diminution in the size of the heart, enlargement of the adrenals, degenerative changes in the alimentary canal, diminution of blood volume, anaemia, acidosis and occasionally oedema and degeneration of a variable number of cells of the central nervous system.

Beri-beri Columbarum, on the other hand, whilst indistinguishable clinically from Polyneuritis Columbarum, shows different pathological features, the chief being the hypertrophy and dilatation of the heart (particularly the right side), fatty degeneration of the cardiac muscle, chronic passive congestion of the abdominal viscera and more marked degenerative changes in the central nervous system and skeletal muscles; in consequence of the more manifest cardiac changes there is a higher proportion of cases showing oedema, hydropericardium and ascites. McCarrison regards polyneuritis columbarum as a true deficiency disease, whilst in Beri-beri columbarum he believes there is superimposed on a pure vitamin deficiency a toxic factor related rather to a relative deficiency of the anti-

neuritic vitamin than to an absolute lack of it in the diet. Where the intake of the vitamin B₁ was completely withheld, uncomplicated polyneuritis resulted.

(The enlargement of the heart found in human beri-beri, though believed by many to be a true hypertrophy of the muscle fibres, is more generally ascribed now (Aaldmeer and Wenckebach,¹⁴⁶ 1929, and others) to oedema of the cardiac muscle which results in interference with its contractile power without disturbance of its excitability.)

The importance of a comparison of human and experimental vitamin B₁ deficiency is obvious since the variable clinical features produced in animals and human beri-beri have been offered as an argument against the view that beri-beri is a deficiency disease.

Tasawa¹⁴⁷ (1914) and Segawa¹⁴⁸ (1914), in comparing the condition produced in birds on a polished rice diet with human beri-beri, reached diametrically opposite conclusions. Tasawa believed the conditions to be essentially different and stressed the importance of such factors as age, sex, climate, muscular work and the kind of rice used in the diet in producing human beri-beri. Segawa concluded that the two conditions were fundamentally the same disease but occurring in

different species of organisms.

That muscular exercise plays a part was shown by Cowgill, Rosenberg and Rogoff¹⁴⁹ (1931), who demonstrated that in dogs there was a more rapid use of the tissue store of vitamin B₁ following muscular exercise.

It has been amply proved (Vedder and Feliciano,¹⁵⁰ 1928, et al) that different kinds of rice have different values with respect to their ability to allow or prevent beri-beri, both in the human being and in experimental animals.

One of the most valuable summaries of the facts bearing on the question of the identity of experimental vitamin B deficiency with human beri-beri was made by Shimazono¹⁵¹ (1931), whose observations extended over a period of years. Amongst the features which he lists as common to the two conditions are: paralysis and pathological changes of the peripheral nerves and muscles; lowering of the minimal blood pressure; slight hyperglycaemia; decrease in concentration of blood catalase; decrease in the difference between arterial and venous blood with respect to oxygen content; increase in blood lactic acid; appearance of oedema in both beri-beri and experimental B₁ deficiency in man with a slighter tendency for oedema to develop

in experimental animals: varying secretion of gastric juice; decreased respiration of surviving erythrocytes; the striking healing action of vitamin B₁ preparations in both conditions.

Findings which are not common to experimentally produced vitamin B₁ deficiency and human beri-beri are summarised as follows: heart changes are more characteristic of human beri-beri; gastro-intestinal symptoms are very variable, but whilst anorexia, nausea and vomiting occur experimentally in both animals and man, severe manifestations tend to occur only in the most acute form; in human beri-beri constipation is more common than diarrhoea; blood cell changes are inconstant and anaemia is uncommon in man and rats in B₁ avitaminosis but common in the bird and rabbit; the basal metabolism is reduced in B₁ avitaminosis in animals and man, whereas in human beri-beri it varies with other conditions, being within normal limits in cases showing only slight motor and sensory loss, but definitely low in cases with marked paralysis; this pathological rise and fall of the basal metabolic rate in beri-beri is rapidly abolished and a return to normal brought about by administration of vitamin B₁. The decrease in body-weight, so constant a finding in

experimental B₁ deficiency, is not a striking characteristic of beri-beri and is found chiefly in the "dry atrophic" form of the disease. This is an important fact, and one of the reasons why many pathological anatomists have not identified human beri-beri with simple vitamin B₁ deficiency; the atrophy of internal organs occurs, however, in inanition, and in the experimentally produced condition is related to the loss in body weight. Lastly, the changes in the adrenal glands are not the same, hyperplasia of the adrenal medulla being constant in B₁ deficiency in all animals but not characteristic in human beri-beri where hypertrophy of the cortex is more constant.

Shimazono concludes: "From this comparison between vitamin B₁ deficiency and beri-beri, it is evident that the two conditions are closely related..... If the cases of experimentally induced B₁ avitaminosis in men were to come to our clinic and their histories were unknown, we would diagnose them as beri-beri."

Another factor of importance which would explain some of the differences between experimental B₁ deficiency and human beri-beri, is that whilst in the former the investigator is able to limit the variables operating in his experiments, the clinical picture of

human beri-beri is almost certain to be a complicated one, in which there may be other dietary deficiencies of a minor or gross nature. In addition, the picture may be further complicated by past or present disease, and by physiological and pathological changes consequent upon age, sex, occupational strain and psychological factors.

Complicating features of other Vitamin Deficiencies.-

The possibility that vitamin deficiencies other than that of vitamin B₁ may be involved in the aetiology of beri-beri must also be considered. There are grounds for believing that the characteristic clinical and pathological picture may be modified profoundly when there is a co-existing deficiency of other vitamins. For example, if a rat is fed on a diet deficient not only in the antineuritic factor but in the whole vitamin B complex, rapid death occurs usually unpreceded by either limb paralysis or dermatitis.

Rosedale¹⁵² (1927) concluded that both rats and pigeons need a factor other than vitamin B₁, in the absence of which beri-beri-like symptoms develop, characterised by oedema and intestinal stasis. A similar view was expressed by Vedder and Williams¹⁵³

(1913) and Williams, Waterman and Gurin¹⁵⁴ (1930). Peters and his colleagues¹⁵⁵ (1930-2) have confirmed the findings of Jansen and Donath¹⁵⁶ (1927) that highly purified preparations of vitamin B₁ do not protect pigeons from loss of weight in the absence of other factors; they concluded that avian beri-beri is a disease involving multiple deficiencies which may account for its varied symptomatology.

Peters¹⁵⁷ (1930-1-2) showed that protection against avian polyneuritis after the 30th day of feeding with polished rice is not afforded by doses of vitamin B₁ which are entirely effective in this respect before this period. Peters inferred from this that the traces of vitamin B₁ in the diet and the vitamin in the tissue reserves are sufficient to prolong life until the development of secondary deficiencies of other vitamin factors, the store of which is depleted more slowly than the antineuritic factor.

Recently Platt and Lu¹⁵⁸ (1936) have stated that the dry atrophic form of beri-beri may be due to an associated deficiency of vitamins A and B₁ and that the degree to which structures are attacked may well be determined by the degree of hypovitaminosis A pre-existing. These observers found that in cases in which the

clinical manifestations present were mainly those of vitamin B₁, the peripheral neuritis was completely cured within a short period; in the more prolonged dry, atrophic forms, treatment had to be extended over a much longer period; in these cases many clinical phenomena referable to vitamin A were frequently present - xerosis of skin and hair, thickening and ridging of the nails, follicular keratosis, desquamation of tongue epithelium, and pyorrhoea alveolaris.

Platt and Yang¹⁵⁹ (1935) showed that in typical mild beri-beri, there is gross unsaturation with vitamin C, whilst the same observers remark: "The occasional occurrence of true pellagra together with certain changes in the mouth and the distribution of pigmentation on the face, hands and feet, has led us to suspect the widespread prevalence in the same patients of insufficiency of the vitamin B₂ factor."

The position is still further complicated by the observations of Hughes, Lienhardt and Abel¹⁶⁰ and Mellanby¹⁶¹ who claim to have produced lesions in the spinal cord and peripheral nerves in animals fed on a diet rich in the vitamin B complex, and that lesions may be prevented by the addition of vitamin A to the diet.

The steps by which beri-beri was deduced to be due to a deficiency of vitamin B₁ have been discussed, but in 1934 Mellanby suggested that the lesions of beri-beri, pellagra and lathyrism may be associated with a vitamin A deficiency. He supports this contention by having produced degenerative changes in the nerves and spinal cord of dogs by diets deficient in vitamin A; these changes were intensified by the addition of ergot to the diet and since plentiful supplies of vitamin A prevented or diminished the toxic effects of ergot, Mellanby suggests that adequacy of this vitamin might have a similar effect in preventing degenerative changes in the central nervous system by other toxins.

With reference to these and similar observations, I believe that the uncomplicated effects of any vitamin deficiency in the diet can only be observed in the early stages of its operation. There is a wealth of evidence in this respect bearing on the early results of vitamin B₁ deprivation. Secondly, it is conceivable, as Theobald¹⁶² (1936) has observed, that gross deficiency of any vitamin in the dietary may result in lesions not merely due to deficiency of that vitamin but to a resultant disturbance of metabolism, the many

factors concerned being imponderable. The inter-relation between vitamins and any interactivity that exists is, as yet, little understood.

The importance of these features must be borne in mind in the study of polyneuritis in this country, where this syndrome may be but one of the many features in a complicated case, in which the correlation of clinical phenomena with nutritional deficiencies may be exceedingly difficult. Some clinicians have accordingly suggested the administration of the antineuritic vitamin as a therapeutic test in cases where such a deficiency is suspected, and believe that a satisfactory response to its use is evidence of a vitamin B₁ deficiency.

It has been claimed that the failure of some cases of human beri-beri to respond to vitamin B₁ therapy is proof that the essential cause of the disease is not a lack of this factor from the diet. But, as has been pointed out, the administration of one single factor would not satisfactorily remedy several deficiencies such as might be present. And secondly, it should be borne in mind that until recently vitamin B₁ was given almost entirely by mouth; the vitamin, possibly through imperfect absorption or insufficient dosage, may not

have reached the most vitally situated lesions soon enough. It has been shown that whereas the oral administration of vitamin B₁ may be ineffective or result only in very gradual improvement, the parenteral injection of the antineuritic factor may result in a very rapid amelioration of symptoms.

In cases in which, for example, dogs and pigeons have completely failed to respond to vitamin B₁ therapy, it is possible that irreparable damage to vital functions has occurred and rendered cure impossible. Similarly, from a clinical point of view, one would not be sanguine of a satisfactory therapeutic response in a case of polyneuritis in which definite irreversible degeneration of peripheral nerves had occurred, even though the polyneuritis were associated with a known vitamin B₁ deficiency.

The recent production of concentrated vitamin B₁ preparations suitable for parenteral administration has made it possible to study the effects of this form of therapy more accurately and should make it possible to contribute more precise knowledge towards the solution of the deficiency-problem in beri-beri and other forms of polyneuritis.

The fact that up to now so many cases of human

beri-beri have responded readily and rapidly to the administration of vitamin B₁ constitutes a powerful argument that beri-beri is fundamentally a deficiency disease and that lack of the antineuritic vitamin is the most important single factor in its aetiology.

VITAMIN B₁.its physiological significance.

The antineuritic vitamin figures so largely in a discussion of the disease beri-beri, and the two are so inter-related that it is impossible to deal with the one apart from the other. The relation of the vitamin to metabolism has already been dealt with, and it may be pertinent to discuss briefly at this stage other physiological properties of the antineuritic factor which may be significant in the study of polyneuritis.

Growth and Maintenance.-

Whilst vitamin B₁ has been found to be essential for normal growth and maintenance, this function has no direct bearing on the present study, and it would serve no useful purpose to discuss it.

Storage and Utilization of Vitamin B₁.-

Animals appear to possess a definite but limited store of vitamin B₁. In the rat and the pigeon this store is exhausted within three or four weeks as judged by the onset of polyneuritis after this time (Vedder and Clark,¹⁶³ 1912; Funk and Macallum,¹⁶⁴ 1915).

Steenbock, Sell and Jones¹⁶⁵ (1923) showed that in

young animals placed on a vitamin B₁ deficient diet, the amount of growth seemed to bear some relation to the vitamin content of the previous diet. Conversely, Pilcher and Sollman¹⁶⁶ (1925) demonstrated that the administration of an excess of vitamin B to pigeons before giving them a deficient diet delayed the subsequent loss of weight. Kinnersley and Peters¹⁶⁷ (1928) produced valuable evidence to support the view that there is a definite daily utilization of the vitamin; not only do symptoms of polyneuritis tend to appear in any given pigeon at a fairly constant date after the commencement of a polished rice diet, but the duration of the cure following the administration of a given dose of vitamin B₁ is related to the size of the dose.

It has been experimentally shown by Osborne and Mendel¹⁶⁸ (1923) that the livers of normal rats contain vitamin B₁ which to a large extent disappears when they are fed on a diet deficient in this vitamin.

According to Westenbrink¹⁶⁹ (1932), the heart, liver and kidney have the highest content of vitamin B₁ under normal conditions, the latter two acting as the main storehouses for this dietary factor; all the organs examined, with the exception of the brain, suffer

great diminution in their vitamin content after the rats have subsisted for five weeks on a vitamin B₁ free diet. These findings were confirmed by Graham and Griffith¹⁷⁰ (1931-32).

Nagayo¹⁷¹ (1923) contended that the demonstration of the presence of vitamin B₁ in the tissues of dead beri-beri patients constituted evidence against the view that the disease is essentially a vitamin deficiency. But it has been shown quantitatively that the amounts of the vitamin in the tissues of a B-deficient animal are distinctly less than those characteristic of the healthy organism. The validity of the deficiency hypothesis should not require that the tissues become absolutely devoid of the vitamin before characteristic symptoms appear, but that the concentration of the vitamin in the various organs shall become less than a threshold or critical value.

Bearing upon the storage of vitamin B₁ in human tissues, the period of development of beri-beri has been determined by Fraser and Stanton¹⁷² (1909), who found that the disease occurred among Japanese coolies after a period of 80-90 days upon a diet consisting mainly of polished rice. Strong and Crowell¹⁷³ (1912) made similar observations in prisoners in the Phillipine

Islands; in their experiments beri-beri developed after 61-75 days.

This factor of vitamin B₁ storage has a definite clinical significance in the study of polyneuritis apart from beri-beri. As will be shown in the discussion on Alcoholic Polyneuritis, it is possible to convert mathematically a "partial" vitamin deficiency (based upon a calculable predicted requirement) into terms of "absolute" deficiency. The results obtained do not differ materially from the findings of earlier workers, in that the symptoms of polyneuritis appeared about the time consistent with the depletion of the stored vitamin.

Loss of Appetite and Inanition.-

Much controversy has arisen in the past in experimental work owing to the difficulty in estimating the results due to true avitaminosis on the one hand, and those due to a concomitant loss of appetite and resulting inanition on the other. It was pointed out by Hopkins¹⁷⁴ (1912) that when accessory food factors were withheld for any length of time, the actual food intake was eventually much reduced; even when the food intake was quantitatively sufficient for the calorific needs of the animal, growth was inhibited. During

avitaminosis there was a deficient utilization of food. Hopkins therefore concluded that the influence of accessory food factors is secondary to their more direct effect on growth processes.

A similar diminution in food consumption during vitamin B deficiency was noted by Chamberlain and Vedder¹⁷⁵ (1911-2), McCarrison¹⁷⁶ (1921), Kon and Drummond¹⁷⁷ (1927) and many other observers.

It has been found by various workers (Marrion, Baker, Drummond and Woollard,¹⁷⁸ 1927, and others) that polyneuritis develops earlier in B₁ avitaminotic animals when forcibly fed than in those allowed to feed naturally. Drummond¹⁷⁹ (1918,1) regarded the anorexia as a natural adjustment in response to the lowered calorific requirement of the animal. Similarly McCarrison¹⁸⁰ (1921) and Peters¹⁸¹ (1930-1-2) also concluded that the loss of appetite occurring during avitaminosis was protective, though the mechanism was not understood.

Many observers believe that many of the features seen during avitaminosis are due to the inanition resulting from the lowered food intake. Drummond considers the fall of body-weight, fall of temperature, hyperglycaemia and the ruffled feathers in the pigeon, to be due to starvation rather than the specific lack

of vitamin B₁. To support this view he has observed that pigeons fed on water and marmite daily, but otherwise starved, present a clinical picture closely resembling that of avitaminosis. It has, indeed, been extremely difficult to disentangle the effects of inanition from those of vitamin deprivation, but from the previous discussions it is obvious that avitaminosis is not to be explained merely in terms of inanition. There is a wealth of evidence to show that vitamin B₁ exerts a very definitely favourable influence on the metabolism of the animal, reflected in heightened metabolism and continued growth and well-being. Boas-Fixsen¹⁸² (1931) showed that the deprivation of either vitamin B₁ or B₂ had an immediate effect on the appetite of the rat; there was a decline within 48 hours, although the previous diet had been adequate; the falling-off and the appetite was greater when B₁ was withheld.

The clinical significance of the loss of appetite accompanying B₁ avitaminosis will be recognised when individual cases are discussed. It will be seen that a rapid return of appetite following the administration of vitamin B₁ is often one of the earliest signs of response to treatment.

The Relation of Vitamin B₁ to Gastro-intestinal
Movements.-

Vedder and Clark¹⁸³ (1912) first observed that atony of the intestine or stasis resulted from prolonged deprivation of vitamin B₁ in pigeons. This was confirmed by McCarrison¹⁸⁴ (1919) who described primary degeneration of Auerbach's plexus following secondary atrophy of the myenteron. Anderson and Kulp¹⁸⁵ (1922), Plimmer and Rosedale¹⁸⁶ (1926) and Rosedale¹⁸⁷ (1929) also noted intestinal atony in pigeons.

A similar condition has been described in rats by Gross¹⁸⁸ (1924), in monkeys by McCarrison¹⁸⁹ (1921) and in dogs by Cowgill et al¹⁹⁰ (1925, 1926, 1930). The last named authors believed the condition to be due to anhydraemia accompanying the vitamin deficiency. Kerr and Drummond¹⁹¹ (1927) on the other hand, were unable to detect any delay in the passage of a barium-meal through the bowel in pigeons rendered polyneuritic by vitamin B₁ deprivation. Still more recently, Chatterjee¹⁹² (1935) noted that in both B₁ avitaminosis and simple starvation there was diminished amplitude, number and intensity of intestinal movements.

Because of the high incidence of pathological changes in the intestinal mucosa in his experimental

animals, McCarrison¹⁹³ (1920 a) postulated that a liberal supply of vitamin B₁ is important in maintaining the health of the intestinal tract.

Moore and Plymate¹⁹⁴ (1932) have noted the frequency of pylorospasm associated with gastric dilatation and haemorrhages, in newly born rats, born of mothers practically deprived of vitamin B₁. The administration of yeast rapidly relieved the symptoms in the surviving rats. The authors have suggested the possible analogy of this condition and congenital pyloric stenosis. Hoobler¹⁹⁵ (1928) described an infantile syndrome which he believed to be indicative of a deficiency of vitamin B₁, the condition being characterised by anorexia, a strange plaintive cry, and a more or less spastic condition of the arms, legs and neck. According to Hoobler, the symptoms are quickly alleviated by the administration of sufficient amounts of vitamin B₁. Soji Takai (¹⁹⁶) notes the great frequency of constipation in breast-fed infants of mothers suffering from beri-beri, or who are subsisting on diets deficient in vitamin B₁; he considers that this "habitual constipation occurs frequently as a symptom of infantile pre-beri-beri", and is readily cured by the administration of vitamin B₁.

Vorhaus, Williams and Waterman¹⁹⁷ (1935) have attempted to classify various states or degrees of vitamin B₁ deficiency, not sufficiently severe to produce the clinical picture of beri-beri. They draw particular attention to hypotonia of the gastro-intestinal tract, and quote a series of eight cases suffering from this condition in whom there was no demonstrable organic disease. Treatment with crystalline vitamin B₁ gave excellent results in six of these patients, in whom there was a marked improvement in appetite and bowel function as shown by X-rays and marked improvement in the constipation.

Shimazono's¹⁹⁸ (1931) observations on the depression of mobility of the alimentary tract and resulting constipation in vitamin B₁ deficiency have been noted.

The Relation of Vitamin B₁ to Gastric Secretion and Digestion.-

Voegtlin and Myers¹⁹⁹ (1919) were the first to suggest that vitamin B might be identical with secretin.. This theory, however, was negatived by Anrep and Drummond²⁰⁰ (1920-1) and Cowgill and Mendel²⁰¹ (1921) who showed that extracts containing vitamin B did not evoke any secretions from the pancreas, liver, or

salivary glands.

There is evidence, however, that in dogs deprived of vitamin B₁ the secretion of gastric juice is diminished and sometimes completely inhibited; this was first demonstrated by Miyadera²⁰² (1921), although Karr²⁰³ (1920) had observed no such digestive disturbances. Danysz-Michel and Koskowski²⁰⁴ (1922) also noted that there was a diminished flow of gastric juice in the pigeon, and that such juice was almost free from pepsin. Many authorities ascribed these results not to the specific vitamin deficiency but to the accompanying inanition and anorexia. The experiments of Webster and Armour²⁰⁵ (1932) are interesting in this connection. They used three dogs having respectively oesophagotomy, gastric fistula and pyloric obstruction, and maintained them throughout in good health and full weight by duodenal feeding. The diet consisted of glucose, casein and olive oil, and all known vitamins were withheld from the diet. In all three dogs there was at first diminution and then cessation of gastric secretion. The addition of powdered brewer's yeast to the diet restored the normal secretory activity of the stomach in three days. The continued repetition of the experiment in one dog eventually

resulted in complete achlorhydria and flaccid limb paralysis. The same workers carried out further experiments²⁰⁶ (1934) in an attempt to exclude as causative of achlorhydria other vitamins than the B complex and to determine, if possible, which factor in the latter is essential for the normal functioning of the gastric mucosa. They concluded that vitamin B₂ was even more effective than B₁ in this respect and that vitamins A, C and D did not appear to be essential for the proper functioning of gastric glands. Cowgill and Gilman²⁰⁷ (1934) also experimented with Pavlov gastric pouch dogs and obtained results suggesting strongly, though not proving absolutely, that a lack of vitamin B in the diet operates in some unknown way to depress the acid-secreting response of the gastric glands to appropriate stimuli. The common association of vitamins B₁ and B₂ in the same foodstuffs is generally recognised. At the same time it is possible that the inhibition of the flow of gastric juice in dogs is due, not to the lack of vitamin B₁ or B₂ but to some stimulating substance which is absent from vitamin B- free diets; it is known, for example, that alcohol can produce an immediate flow of gastric juice. Drummond²⁰⁸ (1918, 1) showed that it was possible to increase the

food intake in animals without influencing growth by the addition of flavouring agents to the diet. This would seem to confirm the original observation of Hopkins²⁰⁹ (1912) that vitamins stimulated appetite in a manner quite different from the action of flavouring agents.

There is, however, evidence to support the view that either vitamin B or the foods containing this vitamin, can influence the secretory activity of the gastric mucosa, and that deprivation of these substances can depress the acid-secreting mechanism.

Clinical interest attaches to this question, from the constantly occurring association of gastro-intestinal disorder and achlorhydria with B-avitaminotic states. Achlorhydria has been reported as occurring frequently in beri-beri by Ohta and Izumita²¹⁰ (1930).

The ^{frequent} association of such conditions as pellagra and sprue with achlorhydria is accepted knowledge. Minot²¹¹ (1929) reported two cases of diabetes with peripheral neuritis and achylia gastrica whose symptoms slowly improved upon taking large amounts of a concentrate of yeast. The association of achlorhydria and the neurological condition of subacute combined degeneration of the spinal cord in which there are evidences of

peripheral nerve degeneration, and the fact that a very large percentage of the cases of polyneuritis investigated by the writer were found to have an associated achlorhydria, are clinical findings which render this association one of aetiological importance. Whilst I am anticipating a future chapter, I draw attention to the question at this point, for though it is more than likely that achylia gastrica can inhibit the utilization and eventual absorption of many dietary factors, including vitamin B, the converse possibility may not be inconceivable that the failure of the gastric glands to secrete acid is a result as well as a cause of a lack or deficiency of this vitamin. Stated briefly, whilst achlorhydria and the pathological condition associated with it may predispose to, or condition a state of vitamin deficiency, conversely, a prolonged vitamin B deficiency may predispose to a state of achlorhydria.

It was pointed out in the previous chapter that in experimental animals deprived of vitamin B, hypotonic conditions of the alimentary canal had been noted. At the same time there is little clinical evidence available which proves that in man the vitamin B complex governs the normal functioning of the bowel, although

it was shown that the administration of the vitamin had produced beneficial effects in some cases. From the evidence quoted on the relation of vitamin B to anorexia, gastric secretion and digestion, it is possible that constipation and intestinal stasis may be due, not to the direct effect of a vitamin B deficiency on bowel function, but to the achlorhydria, gastric atony, and failure to ingest suitable foods.

Vitamin B₁ in natural foodstuffs.-

Vitamin B₁ is widespread and has been detected in almost all natural foods. Since the complex nature of vitamin B was discovered, fresh assays of foods have been required to determine their value with respect to the various components of the complex, particularly B₁ and B₂. The natural foods rich in vitamin B₁ are:- Yeast, cereals and edible pulses, eggs and liver; green leaf vegetables are potent if dry weights are considered. Milk, meat and fish are comparatively poor in this vitamin.

Yeast is the richest source of vitamin B₁ and is unaffected by extraction and autolysis. It is, however, very variable in potency. Brewer's yeast is a richer form of supply than baker's yeast. Marmite is a

commercial preparation of yeast which constitutes a palatable and convenient method of prescribing the vitamin: 1 Gram of marmite contains 130 Cowgill mgn., e.g. B₁.

Cereals. The largest deposits of vitamin B₁ are contained in the embryo or germ; the bran (pericarp and aleurone layer) is next in order of importance; the inner bulk, or endosperm, is very deficient in the vitamin, and its exclusive dietary use will occasion beri-beri in man and polyneuritis in birds. While most vitamin assays on cereals have been done with rice and wheat, it is believed that in all cereals the antineuritic factor is chiefly concentrated in the embryo.

The importance of vitamin distribution in cereals may be recognised by the fact that white flour contains no appreciable amount of vitamin B₁; low grade flour and wheat bran are twice as rich, and standard "middlings" (containing most of the embryo) four times as rich as unmilled grain. To a very slight extent the lack of vitamin B₁ in white bread is offset by the addition of yeast in baking, but the amount added is usually less than 1% of the flour.

Pulses. Dry peas, lentils and certain beans and

peanuts have been found to be rich sources of vitamin B₁.

Eggs are valuable sources of antineuritic factor, which is concentrated in the yolk. Dried eggs have been found to retain unimpaired the valuable anti-beriberi properties of the fresh article.

Meat is comparatively deficient in the vitamin. Ox liver, brain, kidney and heart are richer sources than muscle-fibre. When liver, however, is supplied in large quantities (as in the treatment of pernicious anaemia) it constitutes a rich source. Tissues of the pig have an unaccountably high vitamin B₁ index as compared with other animal tissues; lean pork has been found to be six or seven times as rich in this respect, as beef muscle.

Vegetables. Water-cress and lettuce are twice as rich as cabbage and spinach, but on the whole vegetables have a low vitamin B₁ value when taken fresh, as in salads, with their high water content. Assays on the dried products show them to be rich. The chief value of salad dishes lies in their vitamin A and C content and minerals. Potatoes, though having a low vitamin B₁ value, have a low water content and in that they are taken in large quantities, have an enhanced importance

as a source of the vitamin.

Fruits are poor sources of vitamin B₁.

Milk has a low value for the antineuritic factor and is very variable. On the other hand, it is easier to ingest a large quantity of fluid than to eat an equivalent weight of most solid nutrients. A pint of milk (473 c.c.) contains 1700 mgm.-eq. (Cowgill) - equivalent to roughly 85 international units - which is thought to represent about a third of the minimal requirement of the average person.

Molasses have a very high vitamin B₁ value. The poor negro classes in the Southern States of America subsist chiefly on low-grade corn-meal, pork and molasses - three foods rich in vitamin B₁ - which probably explains the fact that beri-beri is never associated with this community.

Fish is a negligible source of vitamin B₁, but the roes of fish, like seeds, and the eggs of birds, are rich sources.

Miscellaneous: there are now many commercial preparations rich in vitamin B₁. Marmite has been mentioned. "Bemax", "Embo" and Vitavose" are known products, prepared from wheat-germ.

Egg-white, honey, cocoanut, purified sugars and

the endosperms of cereals contain either no vitamin B₁ at all, or only infinitesimal amounts.

Vitamins B₁ and B₂.

Wheat embryo is rich in B₁, poor in B₂.

Milk, green leaves, potatoes, roots, are rich in B₂, poor in B₁.

Egg-white contains B₂ but not B₁.

Miscellaneous properties of vitamin B₁.-

Solubility. Antineuritic substance is soluble in water and is not precipitated by moderate concentrations of alcohol. The latter solvent in varying concentrations has been widely used to extract the vitamin from various natural sources.

Vitamin B₁ present in purified yeast concentrates is not dissolved by ether, ethyl acetate, chloroform, or carbon-tetrachloride. It is soluble in glacial acetic acid and 70% acetic acid or 70% acetone.

Stability to Heat. The resistance of vitamin B₁ to heat in faintly acid or acid media is considerable; under these conditions little or no destruction occurs after exposure to 100°C. for several hours. With higher temperatures there is a progressively increasing

rate and degree of destruction; it is estimated that after heating for two hours at 129°C . the original potency of the vitamin is reduced to one quarter. These observations hold good irrespective of the nature of foodstuff containing the vitamin.

Influence of Hydrogen ion concentration on the stability of vitamin B₁. The vitamin resists hydrolysis with acids, and does not lose its antineuritic properties after heating with 20% sulphuric acid for 24 hours. Vedder and Williams²¹² found that following hydrolysis with 50% sulphuric acid an extract of rice polishings had an enhanced curative potency.

Whilst the stability of the antineuritic vitamin towards acids has been amply confirmed, the action of alkalies leads to its destruction even at low temperatures. The potency of yeast is destroyed by treatment with 0.1 N caustic soda for 90 hours at room temperature, and there is a progressive destruction of the vitamin on heating at 100°C . at decreasing hydrogen ion concentrations.

In addition, vitamin B₁ can withstand dessication for long periods of time - as is demonstrated by its abundant presence in dried foods. Apparently it is

not susceptible to oxidation by atmospheric oxygen, thus differing from vitamins A and C.

Exposure to ozone does not detrimentally affect it, nor does ultra-violet radiation provided it is not prolonged.

Cooking and Baking. Most people derive their main supplies of vitamin B₁ from cereals. In the baking of wholemeal bread or biscuit, the operation is relatively short and as the temperature of the interior of the material seldom rises above 100°C., little, if any, decrease in the vitamin B₁ content takes place. On the other hand, the prolonged cooking of foodstuffs at temperatures much higher than 100°C. leads to some loss of the vitamin. As, in the commercial process of "canning" of foods, much higher temperatures are frequently employed, all canned or autoclaved foods should be regarded as being free from, or deficient in vitamin B₁, unless they have been investigated and found satisfactory.

In the prolonged cooking of vegetables, the vitamin may not be destroyed by heat, but it has been estimated that 30 to 50% passes into the water, which is afterwards thrown away.

In general it may be recognised that town communities who, in winter particularly, consume large amounts of white bread, cakes, scones, buttered toast, potatoes, fish, kippers, doughnuts, pies, pastries and preserved or canned grocery foods, whilst subsisting on a diet of high carbohydrate and calorie value, are partaking of a diet of markedly low value in vitamin B₁.

The Isolation of Vitamin B₁.

The isolation of the active antineuritic substance from rice, yeast and foods known to contain it, constitutes a chapter of historical and chemical interest. A review of the literature, however, would serve no useful purpose here, and only the more important preparations need be mentioned.

Jansen and Donath²¹³ in 1926 (1, 2), in the laboratory in Batavia in which Eijkmann made his fundamental discovery, isolated vitamin B₁ in crystalline form. This preparation was prepared from an extract of rice polishings adsorbed on acid clay at pH5.0 and extracted therefrom by Seidell's^{213a} method (1922, 1). This acid-clay preparation has a two-fold importance: it has hitherto been largely used in Java for the cure of beriberi and as it forms a satisfactory stable preparation of

vitamin B₁, it has been adopted by the (League of Nations) International Vitamin Conference, 1931, as the provisional standard for the antineuritic vitamin B₁. The dosage of Jansen and Donath's crystalline preparation for curative activity has been found to be - pigeon day-dose by mouth, .009 mg; by injection 0.007 mg; rat day dose, 0.005 mg.

Windhaus, Tscheche, et al²¹⁴ (1931) by applying the methods of Jansen and Donath to yeast, were able to isolate an even more highly active crystalline compound, with the formula C₁₂H₁₆N₄O₅, and the identity of these two preparations from rice and yeast seems to be established. The average curative pigeon day-dose, by injection is stated to be 0.0024 mg.

In 1936, attempts to prepare vitamin B₁ synthetically were successful. It was achieved independently and almost coincidentally in America by Williams and Cline²¹⁵, in Germany by Grewe²¹⁶ and in this country by Todd and Bergel²¹⁷ in the Edinburgh University Chemical Research Laboratory. By the latter workers the synthetic preparation was named Aneurin. Its formula was calculated as C₁₂H₁₈ON₄Cl₂S, H₂O (40.6, H5.6, N15.8, S9.0, Cl 20.0%). Aneurin has been found to be a highly active substance which may be administered

orally, intravenously or intramuscularly. Vitamin B₁ is now widely issued in the synthetic form under various trade-names, and as, in most of these preparations 1 c.c. contains the equivalent of 400-500 international units, large scale doses can be given parenterally with convenience and safety. The effects of vitamin B₁ therapy are thereby achieved rapidly, and any possible errors due to malabsorption in the alimentary canal are obviated.

BERI-BERI and HUMAN DIETS.

The aetiology of beri-beri and the significance of the antineuritic vitamin B₁ in its causation have been discussed. Before concluding this chapter there still remain for discussion two important applications of the knowledge acquired in the causation of the disease:-

- (1) The communal occurrence of beri-beri on diets deficient in vitamin B₁, and not necessarily confined to rice-eating populations.
- (2) The relationship of the occurrence of the disease to the degree of the vitamin B₁ deficiency. In this connection I propose to discuss briefly the results of Cowgill's investigations on the "Vitamin B₁ requirement of Man"²¹⁶ (1934) - an intensive and valuable contribution to our present knowledge on this subject.

If it is borne in mind that the thousands of cases of beri-beri which have occurred, and still occur, annually, are characterised clinically by one of the severest forms of polyneuritis known, then the significance of these references to the problems of the present investigations on the aetiology of polyneuritis need not be further stressed.

In southern and eastern Asia, rice is still the staple article of diet of the poorer population. And

it is precisely in these countries - Japan, China, Java, Malay States, the Phillipines and parts of India - that classical outbreaks of beri-beri have occurred. Countless investigators (many of whom have been referred to) have been able to show the association of the disease with the consumption of white, polished, steam-milled rice, i.e., rice from which the outer skin and germ have been removed. Further, it has been shown that where the rice is merely husked, and the germ and outer skin retained, beri-beri does not occur. And in districts where beri-beri is epidemic, the substitution of whole rice for white, polished rice has both prevented and cured the disease.

Vorderman^{217a} whose observations extended over a population of 279,000 people, conducted a survey of Java prisons and noted the incidence of beri-beri relative to the type of rice consumed.-

Type of Rice consumed.	No. of prisons examined.	No. in which Beri-beri occurred.	%	Proportion of cases of beri-beri among total No. of inmates.
1. "Half polished"; $\frac{5}{4}$ of silver-skin adherent	37	1	2.7	1 in 10,000
2. $\frac{1}{3}$ of silver-skin adherent	13	6	46	1 in 416
3. "Polished"; less than $\frac{1}{4}$ silver-skin adherent	51	36	71	1 in 39

These early observations have been repeatedly confirmed since and suggest strongly that when a cereal food such as rice is the main article of diet, the whole unmilled cereal must be employed if beri-beri is to be prevented, and that even in this case the margin of safety is not great. In fact, McCarrison²¹⁸ has pointed out that beri-beri may occur where the diet consists of whole rice if it is not supplemented by other foods containing vitamin B₁, i.e., a diet of whole, untouched rice does not consistently provide enough vitamin B₁ for a man. Whilst these observations rather shake the belief that beri-beri would be eradicated by the abolition of the steam-milling of rice, it does not upset the assumption that, since polished rice is poorer in vitamin B₁ than is whole rice, given the same but inadequate supplements, beri-beri is more likely to occur on the diet containing polished rice than on that containing whole rice. It has also been shown that there are various qualities of rice, and that rices may be ranged in accordance with their vitamin B₁ value. McCarrison's²¹⁹ (1924) further observation that the vitamin B₁ content of unpolished rice may, by washing, be reduced to that of milled rice, may help to explain some of the puzzling

epidemics of beri-beri in India. This "washing-out" of vitamin B₁ from rice has its counterpart in the boiling of cereals, vegetables and other vitamin containing foods in this country; the "water-soluble" nature of this vitamin must not be overlooked.

Beri-beri then, may occur in spite of the presence of a certain amount of vitamin B₁ in the diet. Thus, relatively undermilled rice may be associated with the disease, and attention must be given in such cases to the amount and nature of supplementary foods used in the same diet. Human beings seldom live on rice alone, and the usual additions to the diet of other foodstuffs has rendered difficult the absolute correlation between the incidence of human beri-beri and the vitamin B₁ content of the rice consumed. Therefore while it is probably unwise to regard the problems of beri-beri in the East as being purely a question of polished or unpolished rice, clear and convincing evidence has accumulated from tropical countries that the substitution of undermilled for milled rice is the biggest factor both in the prevention and cure of human beri-beri. This pertains not only to the adult forms of the disease but also to infantile beri-beri, as was shown by Wells²²⁰ (1921) in his treatment of

infants with extracts of rice-polishings - an observation which has been repeatedly confirmed since.

The good results obtained with whole rice containing the antineuritic vitamin have also been obtained by the more concentrated preparations of vitamin B₁ which have been used in treatment. At the same time it must be admitted that there is not much evidence in the literature of treatment of human beri-beri being successfully carried out by vitamin B₁ alone without other dietary alterations and additions. It has been pointed out that the diets on which beri-beri has developed, are deficient in several factors besides vitamin B₁, and that though the polyneuritic manifestations are primarily due to deficiency of this vitamin, some of the other symptoms grouped under the heading of "beri-beri" may quite well be due to other deficiencies; the possibility of a concomitant deficiency of vitamin A contributing to the prolonged form of "dry" or atrophic beri-beri, as distinct from the "wet" form of the disease, and the possible shortage of proteins as a factor in the production of the oedema of "wet" beri-beri are two instances which may be quoted. Therefore, most observers and clinicians agree that while major importance must be paid to vitamin B₁ as the principal

curative agent, success is most likely to be achieved by the provision of a good all-round diet containing abundant proteins, minerals and other vitamins.

Beri-beri in non-rice-eating peoples.

Though not so common, outbreaks of beri-beri have occurred in wheat-eating populations, where white, wheaten bread is the staple article of diet. Here again the incidence of the disease depends on the vitamin B₁ nature of the foods used to supplement the diet. A few out of the many instances where beri-beri has occurred in these circumstances may be quoted.

The people of Newfoundland and Labrador subsist very largely on wheaten bread during Winter and Spring, and beri-beri is frequent. Yet, before the advent of "civilized" methods, when "brown" flour was the only kind used for the baking of bread, the disease was almost unknown. Little²²¹ (1912) has related how in 1910 a ship ran ashore laden with a cargo of wholemeal flour, which the inhabitants of that district subsequently used for their bread for a considerable time; no case of beri-beri occurred amongst these people for a year. Aykroyd²²² (1930, 2) has furnished an interesting report on beri-beri in Newfoundland and Labrador;

he has shown the increased incidence of the disease in Winter and Spring, reaching its peak in May, and has correlated this with the seasonal variations in diet. In Winter, it becomes almost impossible to procure fresh meat and vegetables, and the staple diet becomes one of white bread and tea. In the families able to afford the luxuries of meat, potatoes, vegetables and larger amounts of peas and beans, beri-beri hardly ever occurred, although white bread was eaten in equal amount.

Prior to 1894, beri-beri was a very rare disease on Norwegian ships; the staple article of diet was biscuit made from rye flour, in the milling of which the germ is not removed. In a misguided attempt to improve seafaring conditions generally, bread baked from white wheaten flour was substituted and beri-beri, according to Holst²²³ (1911-12) became a frequent disease in the Norwegian mercantile service, although other foods such as meat and fish were used to supplement the diet. Holst relates the story of one sea-captain who refused to eat the "new-fangled" white bread, and provided for his own private use a supply of the customary rye-flour. When his own men were stricken with beri-beri he was able to cure them by supplying

them with rye biscuit from his private supplies. But owing to increasing demands he was finally compelled to husband his rye-flour in order to preserve his own health!

Among Europeans the vitamin B deficiency in white wheaten bread is usually compensated for by a mixed and varied diet of other food-stuffs rich in the vitamin. Under war-time conditions, or as a result of poverty or ignorance, when the bulk of the diet is made up of canned and preserved foods, beri-beri is apt to occur. Wilcox,²²⁴ (1916, 1, 2) for example, has drawn attention to this factor as the cause of outbreaks of beri-beri which occurred among our troops in the Dardanelles and Mesopotamia in the late war. It is significant that in the latter campaign the cases were confined to the British troops, whilst the Indian soldiers remained free. Examination of the respective diets reveals the illuminating fact that the native soldiers received quantities of a coarsely ground whole wheat flour called "atta", and generous rations of "dhal" or dry pulses, now known to be rich in vitamin B. Hehir²²⁵ (1917) has written an interesting account of medical experiences during the siege of Kut-el-Amara between December 1915 and April 1916. During the early part

of the siege there was an outbreak of beri-beri amongst the British troops, the disappearance of which was marked by an outbreak of scurvy amongst the Indian troops. Whilst the epidemic of beri-beri was in progress, the British troops were receiving white wheaten flour, but as supplies were running out they were compelled to use the coarsely milled but germ-containing "atta" or barley-flour of the Indians; the enforced change of diet resulted in the disappearance of beri-beri. On the other hand, the British throughout had daily rations of meat, including horse-flesh, and did not develop scurvy, whilst the Indian troops, existing now almost entirely on vegetarian diet, suffered severely from this disease.

The above experiences emphasize the importance of the inclusion of the germ and bran of wheat in the baking of bread or biscuit when, for any reason, a restricted diet is enforced. Even in modern conditions where so many people rely to such a large extent on canned and preserved foods from the grocery stores, a change from the more delicate white loaf to the coarser, brown or wholemeal bread would be a definite safeguard against the occurrence of some degree of vitamin B deficiency.

The influence of a yeast drink as a protective and curative measure for beri-beri is shown by the following observation. Bray²²⁶ (1928-29) describes the experience of the inhabitants of the island of Nauru in the Pacific Ocean. Their diet consisted mainly of fish and coconut products, including "toddy", a fermented beverage prepared from the coco-nut palm. This island has been governed, since the Peace, under mandate by the Commonwealth of Australia and the making of toddy was prohibited. To replace it, the natives used more imported foods, white flour, sugar and canned foods. The infantile mortality rose to alarming heights, and the chief contributory factor was found to be infantile beri-beri. Toddy-yeast was used as the principal therapeutic agent actually to cure the babies. It may be that many native races depend for protection against beri-beri on similar home-brewed fermented drinks.

Most of the above examples represent the occurrence of beri-beri on diets obviously deficient in foods containing the antineuritic vitamin. That the disease may be associated with diets containing a varied selection of foodstuffs containing, at first sight, no gross deficiency of vitamin B₁, is instanced by the following details of diets issued to a camp in a Mediterranean

area during the late war. For comparison, other diets, closely similar, but satisfactory in that beri-beri was not occasioned by them, are also given. The amounts of the various constituents are expressed as "ounces per week".

ø <u>Foodstuff.</u>	Nos. expressing approx. value in preventing Beri-beri. Wheat-germ = 100.	<u>Diet A.</u> (Beri-beri producing)		<u>Diet B.</u> (Satis- factory)	<u>Diet C.</u> (Satis- factory)
		A1.	A2.		
Foods deficient in Vitamin B ₁					
Rice	-	28		21	28
Bread (white flour)	-	224	224	112	168
Jam	-	-	-	7	7
Sugar	-	14	14	7	
Cheese	-	14	14	14	
Dry fruit	-	-	-	14	
Salt fish	-			20	
Margerine, butter or oil	-	14	14	7	3.5
x = Total No. of oz. weekly of foods deficient in anti-beri-beri factor		294	266	202	206
Foods richer in Vitamin B ₁					
Oatmeal	10	-	-	14	14
Fresh Meat or Bacon	10	42	42	30	42
Peas, Beans, Lentils	50		28	14	21
Potatoes or fresh vegetables	5	14	14	42	28
V = Total No. of Oz. weekly of foods containing anti-beri-beri factor		56	84	100	105
RATIO V/X		0.2	0.3	0.5	0.5

(ø These tables were published by Major L. Braddon, R.A.M.C.,

and are taken from the Medical Research Council's Report - "Vitamins - a survey of present knowledge, 1932".)

Beri-beri was associated with diets A1 and A2, but no cases were reported as occurring with diets B and C. Although in many ways similar, it will be noticed that there was a preponderance of cereal food (rice and white bread) in diets A1 (252 ozs. weekly) and A2 (224 ozs. weekly) as compared with diet B (133 ozs.) and diet C (196 ozs.); and secondly that there was a smaller proportion of vitamin B₁-containing foodstuffs. A1, 56 oz. weekly; A2, 84 oz.; B, 100 oz.; C, 105 oz. If the ratio - number of oz. vitamin containing food/number of oz. vitamin deficient food is calculated for the four diets, a series of values is obtained rising from 0.2 for diet A1 to 0.5 for diets B and C, which serves to give a rough indication of the value of a diet for the prevention of beri-beri.

From a purely clinical point of view and particularly as regards polyneuritis occurring as a "fragment" of the beri-beri picture, the following observation made at the time is noteworthy. After the diagnosis of beri-beri had been substantiated for certain men receiving Diets A1 and A2, "a careful search among the

healthy men of the same community revealed a widespread abnormality in knee-jerks and other nervous reflexes".

This observation serves to indicate that the normal health may be undermined by a dietary deficiency before any symptoms are apparent to the casual observer or to the individual himself. It shows equally the importance of recognising a state of pre-beri-beri and searching for the presence of clinical signs before they have become outwardly apparent, in all cases where a diet deficient in vitamins is suspected.

The work quoted in the above paragraphs substantiates the view that beri-beri is conditioned by diets deficient in vitamin B₁. Reference has been made to the earlier observation that the amount of vitamin containing foods and their relation to the diet as a whole bears a further relationship to the onset of beri-beri. I propose now to carry the investigation a stage further and to refer to a more recent hypothesis, that the vitamin B₁ requirement of man may be calculated quantitatively and that, if the minimal calculable amount per individual is not maintained, beri-beri will result.

The Vitamin B₁ Requirement of Man.

For the purposes of this thesis it will suffice to summarize briefly the results of an intensive research by Cowgill, extending over many years, which is admirably described in his monograph bearing the title of this section²²⁷ (1934). This work owed its origin to an interesting observation made many years ago that the rat requires more vitamin B₁ per unit of weight than the dog; this was amplified by the late Professor T.B. Osborne by the hypothesis that "man cannot possibly require as much vitamin B₁ per unit of weight as the rat; if such were the case all of us would die early from beri-beri". It was reasoned, therefore, that if some common relationship could be found to hold for quantitative data derived from several animal species with respect to vitamin B₁, there would be some justification for believing that a similar relationship holds for the human species. Measurements were accordingly made of the amounts of a given vitamin B₁ concentrate required by different sized mice, rats, pigeons and dogs. As various species of animal respond to vitamin B₁ deficiency in different ways (e.g. polyneuritic symptoms are produced readily in the pigeon and dog, whilst anorexia and inanition are often the earliest

symptoms in the mouse and rat), all the recognised early clinical manifestations of vitamin B₁ deficiency were used as criteria. Only Vitamin B₁ preparations of known value and concentration were used. In brief, the appearance of anorexia, the influence on growth, the first signs of polyneuritis and other clinical manifestations were taken as evidences of deficiency in conjunction with the Protective, Weight-maintenance and Curative tests. In so far as no one test has hitherto given entirely satisfactory results for all species, authority is given to Cowgill's work in that all were employed and the results correlated.

The groups of data denoting the minimal amounts of the antineuritic vitamin required to maintain the health of the various species were studied and a mathematical relationship common to all of them was discovered. The formula thus derived indicates that the vitamin B₁ requirement is determined by three important variables:-

1. The body-weight.
2. The total metabolism or calories.
3. The maximal normal weight of the species.

Experiments designed to test the implication of the formula were conducted on pigeons and dogs, and

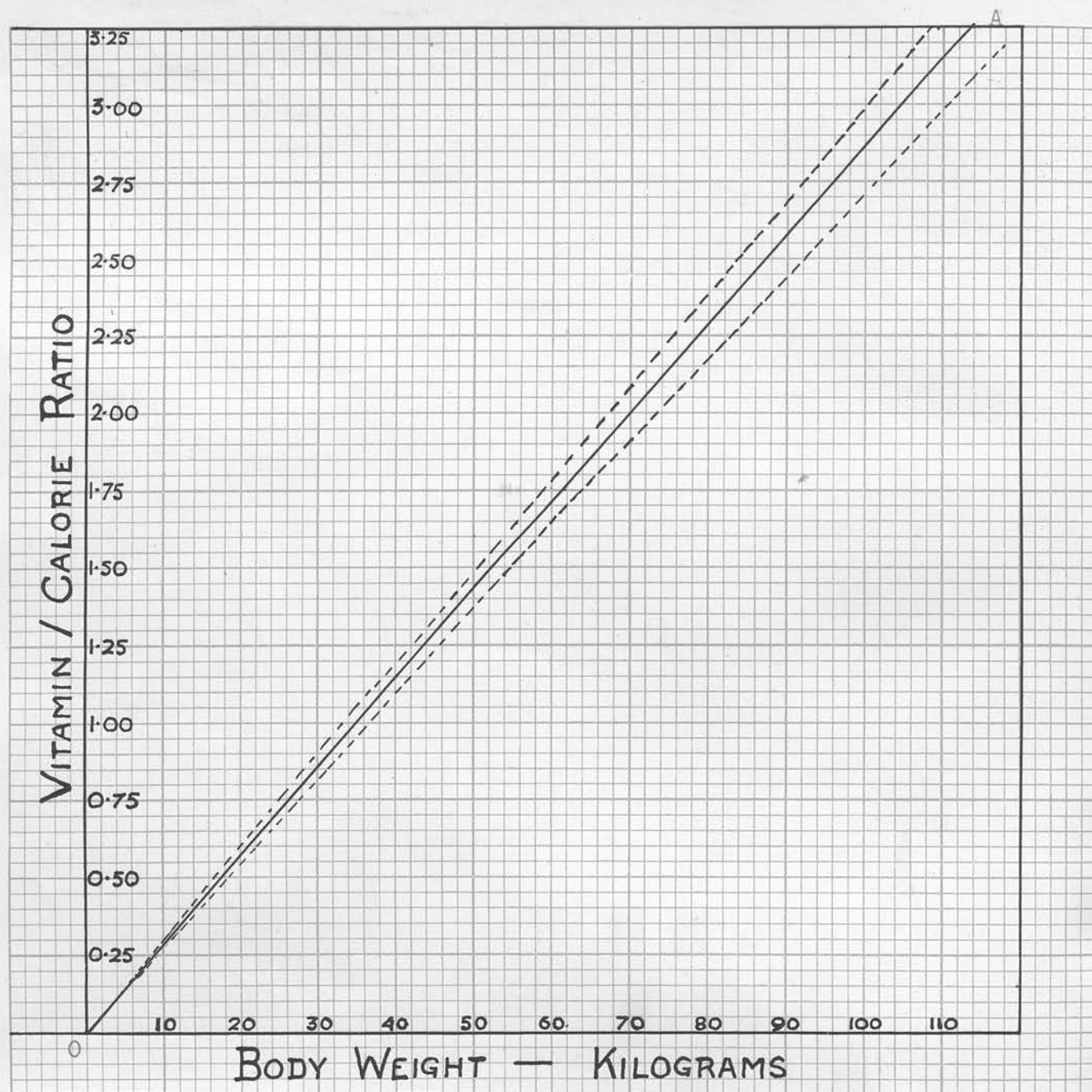
confirmation obtained.

It was obviously not feasible to study the same problem directly in the human species, as beri-beri would have been the inevitable result of a serious and prolonged shortage of the antineuritic vitamin in the diet. But from the data obtained from a study of the mouse, rat, pigeon and dog, a formula applicable to the human species was derived. The final formula arrived at by Cowgill for man was expressed as:-

$$\frac{\text{Vitamin B}_1 \text{ Milligram equivalents (Cowgill)}}{\text{Calories intake}} = 0.0000284 \text{ Weight in Grams}$$

$$\text{or, more simply, } \frac{\text{VIT}}{\text{CAL}} = .0000284 \text{ Wt. (Grams).}$$

This expression was tested by a study of the vitamin B₁ content of numerous human dietaries, (a) which were known to have been used by persons who developed beri-beri, and (b) which were not associated with the appearance of beri-beri. The amounts of vitamin estimated to be furnished by these various diets were compared with the requirements of the individuals who subsisted upon them in order to determine their adequacy as predicted by the above formula. The results of such a study were also compared with the facts known concerning the incidence of beri-beri in the respective groups



The Human Requirement of Vitamin B (B_1) - Prediction Chart. The adequacy in vitamin B (B_1) content of a given human diet for individuals of different body weights may be estimated by reference to this chart. The plot indicated by line OA represents the probable minimum vitamin B (B_1) requirement referred to body weight. The area between the dotted lines represents a zone of uncertainty; for discussion of this area see the text. If the Vitamin/Calorie value of the diet for a given body weight falls definitely above line OA, the ration is deemed adequate with respect to vitamin B (B_1); if the plot proves to be appreciably below the line, the vitamin requirement is not satisfied by this diet and beriberi should occur provided the period of subsistence on this ration is sufficiently extended; if the plot is close to line OA, or between the dotted lines, the diet may be considered as "borderline" in character.

studied. A study of Cowgill's monograph reveals the excellent agreement of the predictions, based on his formula, with the facts concerning the presence or absence of beri-beri. Of the beri-beri groups studied, only 8.6 per cent. failed to show good agreement.

For the clinical application of the formula as a test of the vitamin B₁ efficiency of a diet, a detailed and accurate knowledge of the diet in question, as regards the measured amounts of all the foodstuffs used, is essential. From this are calculated - (1) the daily calorific intake (representing metabolism) and (2) the daily intake of vitamin B₁; nearly all known foodstuffs have been assayed by numerous workers as regards their vitamin B₁ content, and tables (published in most authoritative works on vitamins) may be referred to for determining the vitamin index of the various foods. Different workers have expressed these values in various "Units", but they may all be re-expressed in International or other units by the following table:-

1 International unit is equivalent to:	(4 Micrograms Jansen-Donath
	(Crystalline vitamin.
)1 Roscoe unit.
)4 Sherman et al. Units.
	(20 Milligram-Equivalents
	((Cowgill)).

Cowgill's "Prediction Chart", which is a graphic representation of the VIT/CAL ratios for various body-

weights furnishes a simple method of testing the vitamin B₁ adequacy of a diet for the particular individual concerned. For example, assuming a dietary yields a daily calorific value of 2200, and vitamin B₁ value of 4,640 mgm.-eq. The VIT/CAL ratio equals 2.11. Reference to Cowgill's prediction chart indicates that a diet with a VIT/CAL ratio of 2.11 would be just adequate for a person weighing 70 kilograms; for an individual weighing slightly more, it would be "border-line", whilst if the individual weighed appreciably more, the diet would be inadequate in vitamin B₁ content and beri-beri would tend to occur if subsistence on it were prolonged.

A few instances of the application of Cowgill's formula to various diets associated and unassociated with outbreaks of beri-beri may be quoted. Some of them furnish more precise details of diets to which reference has been made in the previous section which conditioned outbreaks of beri-beri.

VITAMIN B₁ INDEX VALUES OF

FOODS IN COMMON USE.

F o o d .	Index Value in Cowgill Mgm.-eq. per Gram.	Calorie Index Cal./Gm.
Barley, husked	20	3.50
" pearled	3	3.55
Corn, whole kernel	20	1.01
Corn meal, new process	5	3.56
" sweet, canned commercial	10	0.98
Indian flour, pure unbleached	23	3.50
Macaroni	3	3.58
Oatmeal	22	3.99
Rice, brown	20	3.50
" polished	1.6	3.51
" polishings	84	4.23
" whole, parboiled	15	3.50
Wheat, bran	40	
" flour	3	3.53
" germ	130	
" bread, white, water	2.1	
Bean, haricot	20	2.70
Lentils	26	
Peas, split	26	
" raw, ungraded	15	1.00
" canned, in human diets	8	0.55
Almonds, ground	20	6.47
Cocoanut, ripe	4	5.90
Hazelnut	40	7.10
Nuts, in human diet, kind not stated	20	6.50
Asparagus	14	0.29
Beet	2.4	0.46
Carrot, raw	3.3	
" boiled	2.5	
Onions	2.7	0.49
Parsnips	14	0.65
Potato, raw white	4	
" in human diets	3.8	0.97
Radish	6.2	0.29
Turnip/		

F o o d	Index Value in Cowgill Mgm.-eq. per Gram.	Calorie Index Cal./Gm.
Turnip	2.4	0.39
Cabbage	4.0	
Cauliflower	2.4	0.31
Celery	1.0	
Greens, raw turnip	11	0.29
" in human dietary, kind not stated	10	0.29
Lettuce, garden	5.0	
Rhubarb	2.4	0.23
Spinach, raw	11	
" cooked 15 mins.	4	
" commercial, canned	1.7-2.0	
" in human dietaries	2.4	0.24
Tomato, pulp	2.2	
" Juice, commercial	2.8	0.17
Watercress	5.5	0.22
Apple	2.2	0.63
Apricot, fresh	2.2	0.58
" dried	6.7	2.78
Banana	3.9	
Grapes, Malaya	2.6-3.3	
Lemon, pulp	3.3	0.44
Orange, pulp	5.6	0.51
" juice	2.2	
Peaches, fresh	2.2	0.41
" canned	2.2	0.47
Peas	1.8	
Raisins	7.0	3.45
Strawberry	2.2	0.39
Beef, heart	15	2.48
" brain, cerebrum	13	1.20
" liver	32	1.29
" muscle	5.2	
Chicken, liver	10	1.37
" muscle	5	1.10
Pork, liver	10	1.26
" fresh, lean muscle	37	2.50
" smoked ham	37	3.00
" pork sausage	24	4.50
" bacon, smoked, med. fat	18	6.25
" salt pork	14	7.10
" fat, lard	11	9.00

F o o d.	Index Value in Cowgill Mgm.-eq. per Gram.	Calorie Index Cal./Gm.
Sheep, brain	7.0	1.30
" muscle, "mutton"	5.0	2.00
Veal	5	1.70
Fish, fresh, in human diets	4.5	1.00
Hen's egg: solids, commercial	20	5.42
" " yolk, raw	6.5	
Butter (from cow's milk)	8	7.69
Cheese, kind not stated	2	4.17
Cow's milk: malted	33	3.89
" " skimmed, dried	13	
" " " fresh	2.4	
" " whole, dried	20	5.08
Cream, as purchased	4.2	2.0
American women (human milk)	2.4	0.62
Honey	0	3.26
Molasses, cane	150	2.87
"Liver 343 (Lilley) powder"	107	
International standard adsorbate	2,000	
"Adsorbed Vitamin B (Lilly) 889071-C"	4,500	
"Beemax"	124	
"Embo"	132	3.75
"Vitavose"	68	3.72
Yeast, bakery, dried, No. 2938	70-100	
" brewery, dried	180-200	
"Marmite"	130	
Yeast Vitamin Powder (Harris)	1,000	

Vitamin B₁ contents of the Diets fed to Parties
I and II of the Fraser and Stanton 1907-8
Experiments (from Cowgill, 1934).

Group	Dietary Component	Amount daily	Vitamin B ₁ index	Vitamin B ₁ content	Calories (approx.)
		Grams		Mgm.-Eq.	
I	White rice	604	1.6	966	2,120
II	Parboiled rice	604	10	6,040	2,114
	(Dried salt fish	120	8	960	420
	(Onions	50	2.7	135	25
	(Potatoes	50	3.8	190	49
Both)Cocoanut oil	24	8(?)	192(?)	216
	(Cocoanut	39	4	156	230
	(Tea	3	0	0	0
	(Salt	3	0	0	0

	Group I.	Group II.
Total vitamin daily ^{Cowgill} (mgm.-eq.)	2,599	7,673
Total calories daily	3,060	3,054
Vitamin/Calories	0.85	2.51
Weight for which VIT/CAL just adequate	30 Kgm.	88 Kgm.
Weight of men in these groups	45 Kgm.	45 Kgm.

The above are the data of the historical experiment of Fraser and Stanton in 1907-1908, by which they showed conclusively that beri-beri was definitely associated

with a diet consisting almost entirely of polished rice. Three hundred Javanese labourers were the subjects of the experiment, and all cases of beri-beri were excluded. The men were divided into two groups, and the rations supplied were identical except that in Group I, white polished rice was the staple article of diet, whereas Group II received parboiled rice. The first case of beri-beri appeared in Group I on the 89th day. After several cases had been observed, polished rice was discontinued and no new cases appeared thereafter. No member of Group II, where ^{the} staple food was parboiled rice, developed beri-beri. The feeding conditions were then reversed with respect to the polished and parboiled rice. After a somewhat longer period, members of Group II (now eating polished rice) were affected with beri-beri, whilst Group I remained free. The association of beri-beri with the too liberal use of polished rice was thus established.

It has since been shown that the parboiling process distributes throughout the endosperm the vitamin normally located in the pericarp and germ of the rice kernel, though there is a slight loss of vitamin through diffusion into the water in which the rice is parboiled.

Study of the diet table shows that VIT/CAL ratio in Group I was 0.85; reference to Cowgill's prediction chart shows that this is adequate only for a body weight of 30 kgm., whereas the average weight of these men was 45 kgm., and required a diet with a VIT/CAL ratio of 1.25. The diet was markedly deficient in vitamin B₁ and should have permitted the development of beri-beri, which it did. The VIT/CAL ratio of Group II was 2.5, adequate for body weights up to 89 kgm. As the average body-weight was 45 kgm. this was doubly adequate. On this diet (of parboiled rice) beri-beri, therefore, should not and did not develop.

A second ratio may be calculated. The men weighing 45 kgm. required a diet containing sufficient vitamin B₁ to give a VIT/CAL ratio of 1.25. Actually the polished rice diet had a VIT/CAL ratio of 0.85, i.e. 68% adequate or 30% inadequate with respect to vitamin B₁.

The Vitamin B content of the diets used by the British Indian Native Troops at Trincomalee before and after the Beri-beri epidemic of 1900-1901.

(Braddon, 1907, p. 270.)

FOOD	Vitamin Index.	Ration in use during Beri-beri epidemic 1900-1901.			Ration introduced in 1901 and associated with disappearance of epidemic.		
		Amount daily.	Vitamin B ₁ content.	Calories (approx.)	Amount daily.	Vitamin B ₁ content.	Calories (approx.)
		Grams.	Mgm.-Eq.		Grams.	Mgm.-Eq.	
Rice	1.6	906	1,450	3,180	453	725	1,590
Attah	23	0	0	0	453	10419	1,608
Dhal	23	87	2,001	309	57	1,311	202
Ghee	8	57	456	433	57	456	438
Meat	5	0	0	0	142	710	284
Vegetables	3	0	0	0	170	510	78
Salt	0	45	0	0	28	0	0
Turmeric	0	15	0	0	28	0	0
Total			3,907	3,922		14,131	4,200
VITAMIN/CALORIES		1.00			3.36		
Body weight for which the VIT/CAL is adequate		36 kgm.			118 kgm.		
Average weight of soldier				56 kgm.			

It is obvious from the above data that the rations used in the 1900-1901 epidemic were grossly deficient in vitamin B₁. The VIT/CAL ratio of 1.0 according to Cowgill's prediction chart is adequate only for an

individual weighing 36 kilograms or under, whereas the average weight was 56 kilograms. Beri-beri therefore would be expected to develop, although the calorific value of the ration was high. The ration introduced in 1901 with a VIT/CAL of 3.36 adequate for body-weight of 118 kilograms is doubly ample and should not be productive of beri-beri. The facts agree with the prediction.

Beri-beri in Newfoundland and Labrador Families.

Aykroyd²²⁸ (1930) collected data on the foods eaten by 25 families in Newfoundland and Labrador during a period of six months, including the Winter months of 1928-29. In thirteen families beri-beri appeared; the remaining twelve families did not suffer from the disease. cursory inspection of the two groups of diets reveals them to be practically the same. Detailed estimation of the vitamin B₁ and calorie values of the diets shows that the first had an average VIT/CAL ratio 1.76. The average weight of the individuals who subsisted on this diet was 66 kilograms, and the minimum VIT/CAL ratio adequate for this weight is 1.87. This diet therefore was inadequate for these individuals; subsistence on it for several

months would, according to Cowgill's prediction, be productive of beri-beri, which agrees with the facts. The average VIT/CAL ratio of the diets of the twelve families who did not suffer from beri-beri was 2.06; reference to Cowgill's prediction chart shows that this ratio is adequate for a body weight of 73 kilograms. As the average weight was 66 kilograms, this group of diets was more than adequate in vitamin B₁ content and beri-beri would not be expected to develop, which again is in agreement with the facts.

Dietaries of British Troops in the Mediterranean Area as described by the Medical Research Committee. (Special report series 38, London 1919, pp. 49-68.)

Category of Interest	Associated with Beri-beri.		Not associated with Beri-beri.	
	Diets		Diets	
	A1	A2	B	C
Total vitamin B ₁ per week in mgm.-eq.	29,921	46,913	43,447	48,838
Total calories per week	30,750	30,782	25,102	25,361
Vitamin/Calorie ratio	0.97	1.52	1.73	1.93
Body weight for which this VIT/CAL value is just adequate (kgms.)	34	54	64	68
Average body weight of soldiers taken as (kgms.)	66	66	66	66

According to these results, diets A1 and A2, both of which were associated with beri-beri, were indeed deficient in vitamin B₁; ration A2 was definitely superior to A1, but according to Cowgill's estimate was still definitely inadequate. Diets B and C should doubtless be classified as borderline, or as characterised by only a very slight

factor of safety. It is not stated as to how long these diets were fed but it is obvious that with the vitamin content so close to the daily requirement in these cases (particularly diet B) a much longer period would be needed for use of these rations to result in beri-beri. It seems more than a coincidence that diet A2 should have allowed beri-beri to develop whereas diet B did not, and that the value of the VIT/CAL ratio in the deficient ration should have been so close to that of diet B, which represents practically the daily minimum for these soldiers. Attention is again drawn to the fact that in men on diets A1 and A2 there was a widespread abnormality of knee-jerks and other nervous reflexes in those who did not develop gross beri-beri. The above example also indicates the degree of accuracy of Cowgill's predicted estimate of human vitamin B₁ requirement.

Rations of British Troops at the
Siege of Kut-el-Amara.

Troops using Ration	Category of Interest	Rations issued			
		Jan.22/1916	Feb.5/1916	Mch.4/1916	Mch.11/1916
British Troops	Total Vit. B ₁ per day in Milligrm.-Equiv.	3944	4931-5611	5924	5660-6228
	Total Calories per day	2839	2835	2420	2304
	Vitamin/Calorie Ratio	1.39	1.74-1.98	2.45-2.6	2.46-2.7
	Body weight for which lowest value of VIT/CAL is just adequate (Kgm.)	49	61-69	87-90	87-94
	Average body weight of soldiers taken as (kgm.)	66	66	66	66
British Indian Native Troops	Total Vit. B ₁ per day in Milligrm.-Eq.	8706	8706	5232-11367	4592-9987
	Total Calories per day	2843	2843	2149-2603	2208
	Vitamin/Calorie Ratio	3.06	3.06	2.41-4.36	2.31-4.52
	Body weight for which lowest value of VIT/ CAL is just adequate (kgm.)	108	108	85	83
	Average body weight of soldiers taken as (kgm)	56	56	56	56

As recorded in the previous section, the above
diets were associated in the British Troops with an

outbreak of beri-beri in the early stage of the siege but not in the Indian troops; in the latter part of the siege scurvy broke out among the latter but the British troops were not affected. For the first two months British troops received a cereal ration of white wheaten flour, but from February 5th, one third to one half was replaced by atta and barley flour, used as coarse bread. The beri-beri disappeared on this diet.

Cowgill's comments on these data.- "The January 22nd diet for the British troops was definitely deficient in vitamin B₁ according to these estimations (adequate only for a man weighing 49 kilograms, whereas average weight was 66 kilograms) and therefore should have been associated with beri-beri, as is indeed the fact. The ration issued February 5th is very slightly deficient, if we base our comparison solely on the minimal value of the VIT/CAL ratio which the diet could have, namely 1.74; it will be noticed that the value of this ratio could be anywhere between 1.74 and 1.98 (which have body weight equivalents of 61 and 69 kilograms respectively) and the average is practically identical with the estimated requirement of these men. From these considerations it appears that the diet was

just adequate. Both of the diets issued in March prove to contain sufficient vitamin B₁ (VIT/CAL ratios of 2.46 to 2.7, adequate for body-weight of 87 kilograms whereas average weight was 66 kilograms) and therefore should not have been associated with beri-beri; this agrees with the facts. The rations used by the Indian Native Troops had large factors of safety throughout and therefore should have prevented beri-beri. This agrees with the fact that the disease did not occur among these troops."

These are but a few examples illustrating the application of Cowgill's formula as a means of estimating the beri-beri producing tendencies of a diet. Of countless epidemics studied, only such diets were examined and reported on as were given in sufficient detail in the literature to enable a reasonably accurate estimation of both calorific and vitamin B₁ values to be made.

Two important observations arising from Cowgill's prediction formula are worthy of emphasis, and have since been found to possess definite clinical significance. The formula for man's vitamin B₁ requirement is given as -

$$\frac{\text{VITAMIN}}{\text{CALORIE}} = 0.0000284 \text{ weight in gram.}$$

If foods, such as carbohydrate, with a high calorie value but little or no vitamin B₁ value are added to a diet, the effect on this formula will be to increase the denominator and thus reduce the VIT/CAL ratio, although the diet, as a whole, may appear to be more nutritious. If a person is subsisting on a diet already border-line with respect to vitamin B₁ and, possibly in an attempt to "take more nutriment", increases the diet by the addition of such foods as white bread and pastry, the effect will be to lower the VIT/CAL ratio and thus precipitate the individual into a potential beri-beri condition if that diet is persisted in.

Secondly, a study of the formula indicates how a diet may be gradually reduced to a low general value without a vitamin B₁ deficiency occurring; provided that the vitamin value is reduced in proportion to the calorific value, the VIT/CAL ratio will be kept constant, and the probable concomitant gradual loss of weight will act as a further factor of safety against the development of a vitamin deficiency condition. Viewed in this light, the early experimental observations of several workers previously referred to, that "the loss of appetite and weight in avitaminosis appears to be protective in some manner not at present understood" would seem to

be capable of interpretation. In this connection it is significant that the diets available to the civilian population of Germany during the Great War, and the rations issued in German camps for war prisoners, furnished high VIT/CAL ratios varying from 2.09 to 3.32, and adequate for body-weights of 74 to 117 kilograms. These diets therefore furnished sufficient amounts of vitamin B₁ even when there was a serious lack of food, and widespread under-nutrition (calorie-shortage) prevailed.

Facts relating to Beri-beri: their explanation on the basis of Cowgill's Hypothesis.

Assuming Cowgill's hypothesis to be correct - that the vitamin B₁ requirement of man is dependent on the ratio of this factor to body weight and calorie intake - many facts noted in relation to Beri-beri are capable of explanation.

Sex-incidence. The pre-eminence of the disease in young adult males would seem to have some relation to the generally accepted fact that males have a higher total energy exchange per day - being heavier, consuming more food and having a higher rate of metabolism than females; they therefore require more vitamin B₁.

Under conditions where the diet is border-line with respect to the vitamin, this sex-metabolic difference may be the chief factor in determining the development of beri-beri.

Beri-beri in Pregnancy and Lactation. Du Bois²²⁹ (1924) has observed the increased metabolism in the pregnant female, and in the Orient it is known that women are more susceptible to beri-beri during pregnancy and lactation. Sure²³⁰ (1928) and Evans and Burr²³¹ (1928) have estimated that a lactating rat requires from three to five times more vitamin B₁ to nurse a litter of young than she needs for the maintenance of her own organism. A woman, therefore, whose diet contains only the minimal requirement of vitamin B₁ in the non-gravid state, may be precipitated by the increased metabolic demands of pregnancy into a state of gross deficiency, and beri-beri result. In a slightly different manner lactation, with its necessitous greater demands on both the intake and body store of vitamin B₁ might condition a state of beri-beri in a woman where diet during pregnancy had contained a bare adequacy of the vitamin.

In both pregnancy and lactation the determining variable would appear to be the degree of safety afforded by the diet.

Infantile Beri-beri. The amount of vitamin B₁ present in maternal milk depends primarily on the amount ingested by the mother before, and during pregnancy and during lactation, as was shown by Sure²³² (1928) and Evans and Burr²³³ (1928). When it is remembered that for the first six to nine months of life the breast-fed infant lives almost entirely on milk, which constitutes the only source of (inter alia) vitamin B₁, the main aetiological factor in infantile beri-beri is clear. This is substantiated by the fact that this condition is mainly confined to Eastern races where the common dietaries are either deficient or barely adequate with respect to the antineuritic vitamin; the amount ingested, therefore, makes inadequate provision for secretion through the mammary gland. In a previous section it has been noted that even in the absence of true infantile beri-beri, the infant may show definite signs of vitamin B₁ deficiency by ill-health, constipation, a plaintive cry, anorexia and a tendency to spasticity of the limbs - a syndrome described by Hoobler (1928) which improved on the administration of vitamin B₁.

The Association of Beri-beri with Febrile Diseases.

Attention has already been drawn to the common association of beri-beri with Malaria, Dysentery, Relapsing fever, Enteric and other diseases of a prolonged nature associated with fever; the theory of the infective or toxic nature of the disease arising from this association has also been referred to.

Cowgill's hypothesis makes another explanation possible. Conditions of increased or heightened metabolism demand a greater proportional intake of vitamin B₁. It is therefore possible that two main factors can operate to produce beri-beri in these conditions: (a) heightened metabolism consequent upon the fever which is often accentuated, and which, in the East, is not usually offset by prolonged rest in bed which reduces the energy exchange due to muscular activity, and (b) the use of an "invalid" dietary, which, if not carefully prescribed, is often markedly deficient in vitamin B₁ and other essentials. These two factors may not operate to produce beri-beri in a patient who has developed malaria or other disease whilst in good health following subsistence on a well-chosen dietary. But in a patient whose diet has been border-line with respect to vitamin B₁ previously, the onset of a febrile illness

might, through heightened metabolism and inadequate diet, precipitate the concomitant appearance of beri-beri. In addition, there is the theoretical possibility that the toxic state, per se, might operate in some way to increase the demand for greater amounts of vitamin B₁ than normally required. Conversely, the lack of vitamin B₁ in the tissues might in some way lower the resistance of nervous and other tissues and render them more vulnerable to damage by toxins.

If Cowgill's hypothesis is correct, that the heightened metabolism demands a greater intake of vitamin B₁, then Fraga's²³⁴ (1923) observation that his cases responded well to Neoarsphenamin is also capable of explanation. For any remedy which can eliminate the infection to which the heightened metabolism and increased vitamin B₁ requirement are due must also operate to cure the beri-beri.

The Association of Beri-beri with Dysentery and other diarrhoeal conditions.

The wealth of literature reporting the frequency of the association of beri-beri with Dysentery, Colitis and other similar conditions, is impressive. But, as has been pointed out in previous sections, it is doubtful

whether beri-beri in these circumstances is a direct infective or toxic expression of the underlying primary disease. A patient may be precipitated into a state of vitamin B₁ deficiency during, say, dysentery in several ways:-

1. By heightened metabolism due to fever, as described above.
2. By a poor "invalid" dietary, inadequate in vitamin B₁.
3. By mechanical loss through the bowel of the vitamin taken in the diet.
4. By failure to absorb an adequate amount of vitamin B₁ owing to the associated gastro-intestinal derangement.

At the present time little is known concerning the actual locus of absorption of vitamin B₁ in the bowel, and the factors which govern its absorption. But this assumed failure of absorption is not an unreasonable hypothesis. We know that in certain pathological conditions of the gastro-intestinal tract, there is a failure to absorb many substances, such as Calcium, iron and other minerals, often in spite of a diet adequate in these elements; sprue and idiopathic hypochromic anaemia and coeliac disease may be cited as such conditions. While Castle²³⁵ (1928) showed in his observations on pernicious anaemia that a gastric

abnormality can condition a state of deficiency irrespective of the adequacy of the diet. Secondly, it has been repeatedly shown that parenteral administration of vitamin B₁ often brings about a dramatic response both in experimental and human beri-beri, whilst the oral administration of the vitamin has had little or no effect. It is reasonable to suppose, in such cases, that for some reason the vitamin has not been absorbed from the alimentary canal in sufficient amount to exert its full effect on the tissues concerned. The administration of the vitamin parenterally eliminates this possibility and thereby constitutes a more reliable therapeutic test of a suspected vitamin B₁ deficiency.

POLYNEURITIS, BERI-BERI and VITAMIN B₁:
a summing-up.

Before proceeding to a discussion of individual forms of polyneuritis, it may be advisable at this stage to summarize briefly the outstanding data which have emerged from a review of the salient features of beri-beri, the antineuritic vitamin and the polyneuritic syndrome. Further investigation resolves itself into an application, to certain types of polyneuritis, of the many factors which have emerged from the above study up to this point.

1. Polyneuritis occurs in association with many recognised disease-complexes; the theory that it is a specific manifestation is thereby rendered doubtful, and the possibility that there may be one or more aetiological factors common to many forms is not inconceivable.

2. Polyneuritis is classically seen in the disease beri-beri, whether produced experimentally in animals, or occurring in the human species.

3. Pathologically, the changes affecting the peripheral nerves in beri-beri are degenerative in

nature; similar changes (by some considered identical) are also characteristic of the peripheral nerves in other recognised forms of polyneuritis (such as alcoholic, lead, arsenical and diabetic) and in the early stage of subacute combined degeneration of the spinal cord. Though pathological changes in the central nervous system are described with all these forms, further investigation is required to define the relationship of these to the peripheral nerve-changes; the two processes may be concomitant. On the other hand, there is evidence in many cases that the primary lesions are in the peripheral nerve endings and the cord changes secondary.

4. Beri-beri is either a disease or a syndrome fundamentally due to deficiency of vitamin B₁. Though occurring most commonly in rice-eating peoples, it may occur in any individual or community where there is a gross dietetic deficiency of this factor. There are substantial grounds for believing that lack of digestion or absorption of the vitamin in gastro-intestinal derangement may account for a number of cases.

5. While vitamin B₁ is to be regarded as the main curative agent in beri-beri, certain symptoms are

suggestive of, and may be associated with other food deficiencies, and success in treatment is more likely to be associated with the provision of a diet adequate in all respects.

6. Toxic and infective conditions so commonly associated with beri-beri, whilst important, do not appear to be direct causes of the disease, but appear to be precipitating factors.

7. Whilst further investigations are necessary, beri-beri is known to be characterised by gross metabolic disturbances, and abnormalities referable to the metabolism of carbohydrates have been identified. These consist in both human and experimental B₁ avitaminosis, in the accumulation in the blood and tissues of carbohydrate metabolic by-products (bisulphite binding substances) of which lactic acid, pyruvic acid and methyl glyoxal are important members. The administration of vitamin B₁ removes, or reduces in amount, these substances; this action has been demonstrated in the human subject, and in vitro in brain tissue.

Vitamin B₁ is therefore believed to be a catalyst, and to be concerned actively in tissue respiration and carbohydrate metabolism.

8. The part played in beri-beri by these bisulphite binding substances is imperfectly understood but certain hypotheses may be formulated.-

- (a) They may exert a direct toxic (or metabolo-toxic) action on nervous and other tissues; (not yet proved).
- (b) The affected cells may be deranged through an interruption of their normal metabolic functions (Peters' "true deficiency" theory).
- (c) They may affect the tissue cells in some way as to make them more vulnerable to the action of other metabolites or toxins which might otherwise be harmless.

9. Whilst beri-beri, or B₁ avitaminosis, is characterised chiefly by nervous, cardiac and metabolic disturbances, other phenomena, such as anorexia, inanition, constipation and gastro-intestinal derangements, are commonly associated; lesser degrees of vitamin B₁, particularly if prolonged, may produce varying degrees of ill-health, characterised by some of the above mentioned manifestations without the classical picture conforming to that of typical gross beri-beri. The picture may be still further complicated by manifestations due to deficiencies of other vitamins and essential factors.

10. A hypothesis has been formulated by Cowgill

that the vitamin B₁ requirement of man is determined by the body-weight and the metabolic exchange (expressed as calorific intake). Applied to the study of epidemics of beri-beri, Cowgill's prediction formula appears to possess a high degree of accuracy, but its practical application to cases of polyneuritis as a means of determining the aetiological significance of suspected vitamin B₁ deficiency awaits further investigation.

ALCOHOLIC POLYNEURITIS,

dietary deficiencies as an aetiological factor in its production; its resemblance to Beri-beri.

Ever since alcohol has been associated with a severe and common form of polyneuritis, it has been regarded as possessing a direct neurotoxic action on nervous tissue. Shattuck²³⁶ (1928) first suggested that the polyneuritis might be due to a failure to ingest or assimilate adequate amounts of vitamin B₁, and observed that the condition "might be regarded as beri-beri". Many observers have concurred in this opinion without advancing convincing evidence to substantiate it.

Minot, Strauss and Cobb²³⁷ (1933) investigated a large series of cases of alcoholic polyneuritis from a vitamin deficiency standpoint. They found the polyneuritis associated with beri-beri and chronic alcoholism to be closely related, the main similarities being as follows:-

1. The diets on which the alcoholic patients had subsisted for months or years were deficient in vitamin B₁ and many other essential factors. The diets were composed largely of tea, coffee, bread, butter, scones,

soups, doughnuts, pie, spaghetti. Eggs, fish, milk, meat and poultry figured very infrequently.

2. The polyneuritic symptoms never appeared early following the alcohol habit; many weeks, months, or years elapsed on a prolonged partial food inadequacy (plus alcohol) before the onset of symptoms.

3. The seasonal incidence compared favourably with outbreaks of beri-beri in temperate zones, i.e. in the Winter months. It is known that dietary deficiencies are not so common in Summer, owing to the greater access to fresh foods, less reliance on tinned and canned foods, less alcohol being taken during Summer months and the beneficial effect of sunlight.

4. The polyneuritis was very often precipitated by febrile illnesses, infections (especially of the respiratory tract during Winter), colitis, acute gastritis, etc.

5. Apart from absolute dietetic deficiencies, nearly all the patients suffered from chronic gastrointestinal derangement referable jointly to the alcoholism and to prolonged dietary inadequacies; these included anorexia, nausea, vomiting, diarrhoea,

intestinal stasis, etc., and could contribute to a deficiency state by retarding or preventing assimilation and absorption. Only seven patients out of 57 had a normal gastric acidity; 50% were achlorrhydric compared with the normal average of 12% for patients of the same age and sex.

6. The polyneuritis in the alcoholics was of the same type as, and identical with, that seen in beri-beri: peripheral distribution, analgesia of the skin, tenderness of the deeper structures, painful muscular cramps, wasting and atrophy of muscles tending to contractures, foot and wrist drop, loss of tendon reflexes and eventually trophic changes in the skin, cyanosis and patches of localised oedema. Though in the alcoholic type the onset was more insidious and the polyneuritis less rapid in its spread, and of not such wide distribution.

7. Other evidences of deficiencies were present as would be expected from the character of the diets and gastro-intestinal lesions.

Fourteen out of 57 had skin and other lesions characteristic of pellagra (vitamin B₂ deficiency); several had varying degrees of oedema - regarded by

many as being due in beri-beri to protein deficiency; hypochromic anaemia was very common owing to inadequate intake or absorption of iron; one patient suffered from chronic alcoholism, polyneuritis and scurvy.

8. In beri-beri, the symptoms are mainly referable to the Nervous, Circulatory and Digestive symptoms. The same combination applied to alcoholic polyneuritis, though cardiac derangements were not so severe as in beri-beri; nevertheless dietetic measures ameliorated the latter without specific cardiac treatment being employed.

9. Treatment consisted of prolonged rest, diet rich in proteins, minerals and vitamins; this included 150-250 grams liver pulp, 200 c.c. orange-juice daily, 100 grams muscle-meat, 500 c.c. milk, 12 grams autolysed yeast and extractives, fresh vegetables, fruits and butter, and 60 c.c. cod liver oil; the diet had a low carbohydrate content.

The excellent response to this treatment was eminently satisfactory and, in the opinion of the authors, more rapid in ameliorating the symptoms than any other form of treatment hitherto employed by them.

It will be observed that the authors based their

conclusions as to the resemblance of alcoholic and beri-beri polyneuritis on a comparison of the aetiological and clinical findings, rather than on a specific response to treatment by vitamin B₁. This was hardly possible as outstanding deficiencies of all kinds were obvious from a study of the diets. In beri-beri, on the other hand (in its typical tropical form), the dietetic deficiency of vitamin B₁ is predominant and not hard to seek; nevertheless, even in beri-beri it is known that success in treatment is attained by the provision of a diet of all-round adequacy, particularly rich in vitamin B₁.

Whilst therefore the above investigation indicates the great aetiological importance of dietary deficiencies and B₁ avitaminosis as significant factors in alcoholic polyneuritis (as in beri-beri), it does not prove the case against a direct neurotoxic action of alcohol upon peripheral nerves. All forms of alcohol were, of course, forbidden during treatment.

Strauss (1935)²³⁸ carried this investigation a step further. He argued that if alcohol was directly neurotoxic, then any associated polyneuritis would tend to become progressively worse if the use of alcohol were persisted in; certainly no amelioration of symptoms

would be expected.

A fresh investigation was therefore carried out on ten patients suffering from severe alcoholic polyneuritis, not complicated by febrile illness or decubitus. They were again given diets adequate in all respects of low carbohydrate value - eggs, milk, meat (muscle), fruit and vegetables. Additional supplies of Vegex (18 grams) or 30 Harris yeast vitamin tablets, or 90 grams of dried brewer's yeast were administered daily by mouth; 10 c.c. of a vitamin B₁ concentrate were injected intramuscularly daily, and to supplement the amounts of vitamin A, 10 c.c. of Lilly's liver extract solution were injected intramuscularly each week. By these means it was hoped to overcome any malabsorption from the intestinal tract. In addition, each patient was supplied with the amount of alcohol to which he had been accustomed; this varied from a pint to a quart of pure blended whisky daily throughout the period of the investigation. Any reluctance to ingest the prescribed food owing to associated anorexia was overcome at first by nursing skill and patience and by the "threat" that the usual post-prandial whisky would not be supplied unless the requisite amount of food was taken. Only once did

the need for this resort arise.

This treatment resulted in the recovery of all the patients and there was no difference in the degree or rapidity of recovery of the polyneuritis as compared to controls treated without whisky.

It would appear from the results of this investigation that the administration of whisky in quantities of one pint to a quart per day does not prevent the relief of the polyneuritis associated with alcoholism provided that an adequate nutritious diet with an abundance of vitamins is administered simultaneously. As Strauss points out, the possibility of some impurity in the alcohol previously imbibed being the cause of the polyneuritis is not eliminated. But from this study it would appear that alcohol, per se, does not cause peripheral neuritis through any direct toxic action. Whilst the results do not prove that inadequacy of vitamin B₁ is the principal factor in the causation of the polyneuritis, the following helpful observations emerge:- (1) That in the cases studied there was a qualitatively inadequate intake of food and vitamins, and (2) the results strongly suggest that assimilation or utilization of accessory food may be seriously impaired by the concomitant gastro-intestinal

disorders consequent upon the alcoholism.

The inference that alcoholic polyneuritis and beri-beri are closely related rests again on the close clinical and pathological resemblance rather than on a proved specific response to vitamin B₁.

Critical Review.

The far-reaching importance of Strauss' investigation led to a review of the work by Jolliffe and Colbert and Joffe²³⁹ in 1936. These authors observed that before a pathological lack of vitamin B₁ could be deduced as an aetiological factor of major importance in the causation of alcoholic polyneuritis, the following postulates (in addition to Strauss') must be fulfilled:-

1. The diets must have failed quantitatively and over a sufficient period of time to contain adequate amounts of vitamin B₁ as compared with the normal requirement - basing the latter on Cowgill's prediction formula for the vitamin B₁ requirement of man.

2. The diets of alcoholic addicts without polyneuritis must have contained adequate amounts of vitamin B₁, however long the duration of the addiction.

We have seen in a previous section that Cowgill predicted the vitamin B₁ requirement of man by the formula:-

$$\frac{\text{Vitamin B}_1 \text{ mg. equivalent}}{\text{Calories}} = 0.0000284 \text{ wt. in grams.}$$

and that the accuracy of this formula was tested by computing the vitamin B₁ and calorie content of numerous human diets, associated and not associated with beriberi. A close agreement was found between the theoretical requirement predicted by the formula and the presence or absence of the disease.

This method of calculation was applied to alcoholic diets associated and not associated with polyneuritis. A possible fallacy was seen to exist in assessing the calorie intake. In the case of a person consuming large quantities of alcohol significant amounts may be lost by vomiting or diarrhoea, or by rapid excretion by the lungs or kidneys. Secondly, the metabolic limits of the body to burn alcohol might be exceeded when more than a pint of whisky was imbibed daily, since it has been estimated that the average man cannot oxidize more than 10 c.c. per hour.

Now it has been calculated that the average American diet has a daily vitamin B₁ content of 6847 mg.

equivalents (Cowgill) and a calorie value of 2500. According to Cowgill's formula, the VIT/CAL ratio represented by this diet is $\frac{6847}{2500} = 2.74$, and is therefore adequate for a man weighing 96 kilograms. If this man imbibes daily one pint of whisky, he adds 1000 calories to the denominator, and thus reduces the VIT/CAL ratio to 1.67, which is adequate only for a body weight of 60 kilograms. According to Cowgill's prediction, any person weighing more than this would, in time, show evidence of vitamin B₁ deficiency.

In applying this estimation to the diets of chronic alcoholics, an attempt was made to avoid two possible fallacies; it was decided in calculating the VIT/CAL ratios to compute only those diets the contents of which could be assessed with accuracy, and to calculate three ratios for each diet - one including all the alcoholic calories, one without alcohol and one including an alcoholic calorie value of 1600 irrespective of whether an amount had been consumed having a higher calorie value; i.e., 1600 calories was taken as the daily metabolic limit of the capacity of the body to "burn" alcohol. It was also recognised that many alcohol addicts exhibit clinical manifestations attributable to vitamin deficiencies other than B₁, though

no method of estimating quantitatively the human requirement of other vitamins existed. Owing to the difficulty of correlating quantitatively the intake (or lack of intake) of other vitamins with clinical findings, only subjects (1) with definite polyneuritis and (2) those without polyneuritis were selected for study; those with complicating phenomena referable to other deficiencies were not selected.

Result of investigation.-

Following the application of Cowgill's prediction formula to the above-mentioned two groups of diets, the results were found to be in line with the hypothesis that alcoholic polyneuritis is associated with a vitamin B₁ deficiency, and analogous to beri-beri in this respect. The diets of alcoholics with polyneuritis had VIT/CAL plus alcohol ratios and VIT/CAL plus 1600 (alcohol) ratios below the predicted vitamin B₁ requirement over a prolonged period, in every case.

Conversely the diets of the alcoholics without polyneuritis, though addicts of long duration, had ratios VIT/CAL plus alcohol and VIT/CAL plus 1600 (alcohol) above the predicted vitamin B₁ requirement. Many of this group were fortunate in that they included, often inadvertently, in their diets some food containing

exceptional amounts of vitamin B₁. A bar-tender regularly imbibed ten $1\frac{1}{2}$ oz. "tots" of whisky daily, but each one was taken with $7\frac{1}{2}$ oz. milk (whole). This amount of milk (75 oz.) included in the dietary calculation, increased his inclusive VIT/CAL ratio to 2.85, whilst the predicted VIT/CAL ratio for his body-weight was 2.75. He did not develop polyneuritis. Another excessive imbibor of alcohol regularly took five eggs and two slices of ham for breakfast and two pork chops with bean or pea-soup for lunch - foods all rich in the antineuritic vitamin.

Another interesting observation made during the investigation was the time required on a diet deficient in vitamin B₁ to produce polyneuritic symptoms. Though variable, this was found to be proportional to the percentage of the predicted requirement the patient was taking; e.g. a man with a VIT/CAL ratio equivalent to but 30% of his predicted requirement would develop clinical evidence of polyneuritis earlier than a man having a VIT/CAL ratio equivalent to 60% of his predicted requirement. This observation led to a useful method of calculating the period of "absolute" deficiency of vitamin B₁. Fraser and Stanton²⁴⁰ - whose classical experiment has previously been alluded to -

fed a diet of VIT/CAL ratio 0.85 to a group of labourers whose body-weight required a VIT/CAL ratio of 1.25, i.e. the diet was 68% adequate in Vit. B₁, or 32% inadequate. The first case of beri-beri appeared on the 89th day of subsistence on this 32% inadequate diet -

i.e. $32 \times \frac{89}{100} = 28.5$ days of estimated "absolute" vitamin B₁ deficiency.

It is obvious that the less the percentage of inadequacy (i.e. the nearer to the normal predicted requirement) the fewer the days of "absolute" deficiency of vitamin B₁, and the greater the length of time which would be required on this diet to produce beri-beri: e.g., if a man were subsisting on a diet of only 10% VIT/CAL ratio inadequacy, this would represent $10 \times \frac{89}{100} = 8.9$ days of "absolute" deficiency. Compared with the subjects of Fraser and Stanton's experiment, such a man would take roughly three times as long to develop beri-beri on his diet as the latter, i.e. $3 \times 89 = 267$ days of partial vitamin B₁ deficiency.

This method of deficiency-period-calculation was applied to some of the alcoholic diets and demonstrated the accuracy of Cowgill's formula. Eight cases who did not develop polyneuritis were definitely "border-line" with respect to their VIT/CAL ratios and judged

purely on this reckoning might have developed polyneuritis. But in six of these cases, whose diets were assessed according to the length of time of estimated "absolute" deficiency, it was found that they had not subsisted for a sufficiently long period on a diet of doubtful vitamin B₁ adequacy to develop polyneuritis; their drinking bouts had, in fact, been of too short a duration.

It might be urged still that the case against alcohol having a direct neurotoxic action is not proved, or that the lack of another vitamin, e.g. A, may be affecting the integrity of the nervous system as suggested by Mellanby²⁴¹ (1931) and that the inadequate intake of vitamin B₁ may be coincidental because of anorexia. The most striking evidence against these possibilities is the fact that no alcohol addict with an adequate vitamin B₁ intake (as expressed by the VIT/CAL plus alcohol ratio) showed clinical evidence of polyneuritis. It is true that the group without polyneuritis with an adequate vitamin B₁ intake, imbibed an average amount of whisky per day less than the group with polyneuritis. But the fact remains that they drank an amount of whisky sufficient to cause polyneuritis if alcohol, per se, were the direct cause. Some

of the former patients had taken a pint of whisky daily for periods varying from six months to ten years; one patient had imbibed 23 oz. daily for ten years without developing polyneuritis, whilst another drank less than a pint of whisky daily and developed polyneuritis in ten weeks. Eight patients had regularly taken over half a pint of whisky daily for periods up to forty years, had an adequate VIT/CAL ratio and did not develop polyneuritis.

Jolliffe and Colbert investigated a further series of 28 cases suffering from alcoholic polyneuritis (August 1936).²⁴² These were divided into three groups, and diets of different values prescribed.

Group A received a basal diet with a calorie value of 2190, vitamin B₁, 3680 mgm. equivalents, and a VIT/CAL ratio of 1.7. This was a vitamin B₁ borderline diet for this group, who weighed from 58 to 63 kgms. In addition, they were given autoclaved Vegex, which contains no vitamin B₁.

Group B received the same basal diet of VIT/CAL ratio 1.7 but were given unheated Vegex containing 4050 mgm., eq. of vitamin B₁. The VIT/CAL ratio was thus increased to 3.6, double that of Group A.

Group C received a generous vitamin-rich diet of

3100 calories and 17,250 mgm.-eq. vitamin B₁. The addition of 18 grams of unheated Vegex gave this diet a VIT/CAL ratio of 6.8, four times that of Group A. The therapeutic results were as follows:-

Group A: no improvement of the polyneuritis had occurred at the end of a month. Two patients were given crystalline vitamin B₁ intravenously, and a marked response rapidly occurred as shown by improvement in the sensory phenomena.

Group B: Improvement occurred in all cases during the month.

Group C: Improvement was most marked and rapid in this group, and was believed to be due not only to the large amounts of vitamin B₁, but to the addition of plentiful supplies of other vitamins and a diet richer in protein and 50% higher in calorie value. At the same time the failure of Group A to improve on a diet barely adequate in vitamin B₁, the response of two of this group to intravenous administration of B₁, and the maintained improvement of Group B on the same diet as Group A but with double their predicted requirement of vitamin B₁, indicated that the improvement of the polyneuritis was fundamentally due to the administration of this vitamin.

From the clinical and pathological similarity of alcoholic polyneuritis and the polyneuritis of beri-beri; the demonstration of diatetic deficiency of vitamin B₁ in the diets of alcohol addicts suffering from polyneuritis; the common association of gastrointestinal conditions affecting assimilation and absorption; the seasonal incidence; the precipitating effect of infection; and above all by the response to treatment as observed in the above investigations, the authors concluded that -

1. Alcohol per se is not the cause of polyneuritis in the alcohol addict.
2. Vitamin B₁ deficiency is the cause of polyneuritis in the alcohol addict.

GESTATIONAL POLYNEURITIS.

Its relation to dietetic deficiencies
and vitamin B₁.

The association of polyneuritis with pregnancy has long been recognised. It has been suggested that the condition may be due to toxins, e.g. from septic foci, or the alimentary canal, operating during a period of lowered resistance to infection. The view which has been more widely held is that the neuritis is caused by some toxin or toxins peculiar to pregnancy. The association of the severer forms of polyneuritis with hyperemesis gravidarum, and cures which have been reported on the termination of the pregnancy have lent support to this view.

In 1930, Theobald²⁴³ suggested that cases of gestational polyneuritis in this country might be a form of beri-beri. In support of his opinion he pointed out that the neuritic form of beri-beri in Bangkok was much higher in pregnant than non-pregnant women, and appeared to indicate that increased supplies of vitamin B₁ were necessary during pregnancy; that the symptoms of the polyneuritis in beri-beri and pregnancy were indistinguishable; and that there appeared to be a

definite interrelation of all the toxaemias of pregnancy, which might be explained by a dietetic deficiency hypothesis. Wechsler,²⁴⁴ in the same year, also drew attention to the possibility of dietetic deficiencies causing polyneuritis in hitherto unsuspected cases, including those occurring during pregnancy. The polyneuritic symptoms of pregnancy polyneuritis conform very closely to those of beri-beri and alcoholic neuritis. Many cases have progressed until Korsakoff's syndrome has been manifested - the association of peripheral neuritis with marked cerebral disturbances. Not only is this syndrome associated with many forms of polyneuritis (associated with the intoxications of lead, copper, arsenic and alcohol), but Carmichael and Stern²⁴⁵ in 1931 described the pathology of five cases of Korsakoff's syndrome associated with alcoholism, in which, in addition to degeneration of peripheral nerves, there were pathological changes in the brain and spinal cord similar to those described in pellagra. These observers suggested that there may be a deficiency of some essential factor in both conditions which allows toxins to damage the cells of the central nervous system. The accepted significance of vitamins B₁ and B₂ in the causation of beri-beri and pellagra, and

their association together therefore favoured the views advanced by Theobald and Wechsler, as to the probability of pregnancy neuritis being associated with dietetic deficiencies, particularly of vitamin B.

Further pathological support is afforded by the observations of Berkovitz and Lufkin²⁴⁶ (1932), Luikart²⁴⁷ (1933) and Ford²⁴⁸ (1935), who described post-mortem findings in the peripheral nerves and central nervous systems of fatal cases of polyneuritis associated with hyperemesis gravidarum, similar to the varying degrees of degeneration seen in alcoholic neuritis, beri-beri and pellagra.

In 1933, Strauss and Macdonald²⁴⁹ successfully treated three cases of polyneuritis associated with hyperemesis gravidarum on the basis of the deficiency theory. They were given a diet of low carbohydrate but high protein value, with considerable amounts of vitamins A, B₁, B₂, D and iron. In two of the cases the pregnancy was terminated before treatment was instituted, but the patients responded very successfully to treatment. In the third case treatment was instituted during pregnancy but improvement was equally marked and the patient was able to go to "full term",

when she was delivered by Caesarean section.

A further case was reported in 1933 by Theobald.²⁵⁰ In this case the polyneuritis affected all four limbs, there were absent knee-jerks, muscular tenderness, weakness and wasting, and choreiform movements of limbs and head. She was put on an adequate diet, rich in vitamins A, B, C and D, the polyneuritis disappeared and she "was indistinguishable from a normal person when she came to be confined".

Similar successfully treated cases of pregnancy polyneuritis have been reported by Fonts, Gustafson and Zerfas²⁵¹ in 1934.

Whilst the above cases establish the relationship between gestational polyneuritis and dietary deficiencies in general, no attempt was made to allocate to any particular deficiency a specific part in the response to treatment. A relationship to vitamin B₁ was assumed by the resemblance of the clinical phenomena to the polyneuritis of beri-beri, and the identification of similar degenerative changes in the peripheral nerves.

The more direct association of vitamin B₁ with gestational polyneuritis is afforded by a study of a further five cases treated by Theobald²⁵² in 1936.

The author draws attention to the frequency of polyneuritic

symptoms during pregnancy (not necessarily associated with pernicious vomiting) and the fact that such cases never clear up before delivery but tend to become progressively worse during pregnancy and invariably require hypnotic drugs to relieve pain and promote sleep. In the five cases, typical polyneuritic signs and symptoms were present. The diagnosis of gestational neuritis was confirmed by authoritative neurologists in all cases.

Treatment consisted in the administration of vitamin B₁ (in the form of tablets prepared by Messrs Vitamins Ltd., each tablet containing 150 international units of vitamin B₁, and no other active substance), without any change of, or addition to, the previous diet, or alteration of the environment.

The symptoms were cured, usually within three weeks, by the addition of from 1500 to 2250 units of vitamin B₁ to the daily diet. In two patients the symptoms had been becoming progressively worse in spite of the daily addition of vitamin A (10,000 units) and D (400 units) and calcium lactate, gr. 30, to their basal diets. One patient was refractory to treatment by vitamin B₁ when added to the diet alone. She was therefore given a diet rich in all respects, vitamin A

(50,000 units), vitamin D (2000 units) and vitamin B₁ (2850 units) daily. The polyneuritis rapidly cleared on the imposition of these supplementary factors. It is significant that in this case the neuritic symptoms were the least conspicuous of any of the five patients, yet it took over six weeks to effect a cure.

Jolliffe and Colbert²⁵³ (1936) have since reported the successful treatment of two cases of gestational polyneuritis by the dietary addition of 10,000 milligram-equivalents (500 international units) of vitamin B₁ daily.

Comment.

Though comparatively few cases of gestational neuritis have been treated hitherto by the repair of dietary deficiencies, the above reports support the contention that such deficiencies are the fundamental cause of this form of polyneuritis. Further corroboration is needed before the more specific relation of vitamin B₁ is proved. At the same time the similarity of the condition to the polyneuritis of beri-beri, both clinically and pathologically, the response ~~of the~~ of the above cases to the addition of vitamin B₁ to an

unaltered basal diet, and the failure of the neuritic symptoms to improve following the administration of other vitamins in large amount, lends support to the view that the antineuritic vitamin is the one most concerned. Theobald's fifth case, which did not improve until vitamins A and D were added to the diet (in addition to B₁) in large amount is striking in that the symptoms of neuritis were less pronounced than in the other cases and yet took double the time to cure. In the opinion of Platt and Lu (to which reference has been made), a pre-existing vitamin A deficiency may determine the extent to which nervous tissues are damaged during vitamin B₁ deficiency states; these authors believe that a deficiency of both factors is concerned in the production of "dry" beri-beri, and that "the course of the illness may be protracted". It is regrettable that in Theobald's case the existence of any clinical signs indicative of A-hypovitaminosis is not mentioned.

Observations have been quoted in previous sections, indicative of the need for ample maternal supplies of vitamin B₁ during pregnancy. Probably most important are the increased demands of the growing foetus, and the increased metabolism. If, therefore, a woman is

subsisting on a diet already border-line with respect to vitamin B₁, then the calls of pregnancy may precipitate a condition of inadequacy. A further loss of nutriment by vomiting would enhance the degree of deficiency, and this would be further aggravated by loss of other vital essential factors. It is conceivable that any existing toxaemia due to focal sepsis, or from any source, would still further render nervous and other tissues more susceptible to injury.

Evidence that malabsorption may contribute to a deficiency state during pregnancy is available, but is, as yet, hypothetical. The occurrence of gastro-intestinal derangement and achlorrhya was stressed in cases of alcoholic polyneuritis, as being probably associated with the malabsorption of nutrient factors. In 1932, Strauss and Castle²⁵⁴ noted that there was marked diminution of gastric secretion during pregnancy: 75% of the cases examined showed a tendency to hypo- or anacidity during pregnancy; 80% secreted a higher concentration of hydrochloric acid after delivery; an average taken of the results showed that gastric secretion was three times as great during the puerperium as during the sixth month of gestation. If these findings of impaired gastric function indicate a

diminution in the powers of assimilation and absorption (comparable to that in other anaemia-achlorrhidric states), then an additional factor contributing to a deficiency-state may be deduced during pregnancy.

The result of the above investigations in cases of polyneuritis associated with pregnancy, while awaiting more adequate investigation, appears to establish the relation of the nervous phenomena with other known B₁ avitaminotic states such as beri-beri.

THE TREATMENT OF CLINICAL CONDITIONS BY
VITAMIN B₁ PREPARATIONS.

The treatment of Beri-beri, infantile beri-beri, alcoholic and gestational polyneuritis by diets rich in vitamin B₁, and by preparations of this factor has been discussed.

The principal symptoms of beri-beri have been seen to be referable to the nervous and circulatory systems, and an ill-defined group of phenomena, including anorexia and hypotonic conditions of the alimentary canal. The disturbances of carbohydrate metabolism have also been recognised.

Treatment with vitamin B₁ preparation has therefore been advocated and administered in many nervous, cardiac and metabolic disturbances where an aetiological factor referable to a vitamin B₁ deficiency has been thought to exist. Similar treatment has been prescribed in numerous cases of debility and ill-health where nutritive factors have been concerned. The vast literature on such work tends to be confusing, as the therapy in many cases has not been confined to the study of the antineuritic factor. The response to diets adequate in all respects, and the use of drugs

and minerals (and physical therapy), whilst often indicating that nutritional deficiencies have played a major role aetiologically, have not served to demonstrate the efficacy of any single factor. In some cases vitamin B₁ has been prescribed in the form of yeast, and the results, therefore, are more referable to the vitamin B complex. Until recently most preparations of isolated vitamin B₁ have been extensively administered orally. It is now an open question whether many of the failures of this form of treatment reported in the literature may not have been due to too small a dosage, and failure of absorption in certain gastro-intestinal conditions.

The parenteral method of administration of concentrated synthetic preparations of vitamin B₁ is comparatively new, and the precise position of this therapeutic agent has, as yet, been little explored. The reports in the literature following its use are, so far, encouraging. The majority of references available are mostly based on more conventional methods of therapy, and must be viewed in this light, but are of value in that the vitamin B₁ products used were of recognised activity, and still constitute the principal physiological and pathological method of supply.

The conditions referred to are those bearing on the subject of the present investigation, though pertinent reference is made to the amelioration of certain symptoms other than those for which vitamin B₁ treatment was instituted.

Diabetes and diabetic Neuritis.

Minot²⁵⁵ (1929) observed two cases of diabetes associated with achylia gastrica and peripheral neuritis. The symptoms slowly improved upon the administration of large amounts of a concentrate of yeast. He commented: "One must wonder if achylia gastrica is not a factor which can inhibit the utilization of both the pellagra-preventive (B₂) and anti-neuritic factor (B₁) of vitamin B".

Wohl²⁵⁶ reported a case of avitaminosis in the course of diabetes "with symptoms and lesions of beriberi". The diet was increased from 900 calories to 1900, and vitamin B added in increased amounts. There was marked improvement in the polyneuritis and the power of walking was restored; the case ended fatally through stoppage of insulin treatment. Myelin degeneration of the phrenic and vagus nerves was found post-mortem; the peripheral nerves and spinal cord were not examined.

Gross²⁵⁷ considered that the constipation and intestinal stasis in diabetes might be due to inadequate vitamin B₁ in the dietary, as these conditions did not apparently improve when abundant "roughage" was given. To eight patients he prescribed 500 mgms. of yeast daily with their usual dietaries. Improvement in these symptoms was marked and encouraging; the cases were still "under observation" when the report was written.

Vorhaus, Williams and Waterman²⁵⁸ investigated the therapeutic effects of crystalline vitamin B₁. These authors commented that diminished carbohydrate tolerance was encountered in many nutritional states but was most consistently associated with B₁ avitaminosis. Eleven diabetic patients were given 10 mgms.^x daily of crystalline vitamin B₁ for four weeks. Frequent blood-sugar estimations showed that six of the eleven had an increased utilization of carbohydrates; in five patients no difference was observed. Of the six patients who responded, two were still maintaining the improved utilization (after five to ten months), two maintained the increase for several months, and two reverted to their previous levels of blood and urinary

^x 10 mgms. crystalline B₁ are equivalent to 4000-5000 international units.

sugar as soon as the vitamin B₁ was stopped. The authors concluded that in 54.6% of the cases observed there was a relationship between the intake of the vitamin and increased carbohydrate utilization.

Various Neurological Conditions.

Pellagra.

Though the major manifestations of this disease are believed to be due to vitamin B₂, the common association in foodstuffs of this factor with vitamin B₁ has led many observers to believe that the latter plays a part in the production of some of the nervous symptoms and lesions. Zimmerman, Cohen and Gildea²⁵⁹ treated an alcoholic pellagrin with a parenteral vitamin B₁ concentrate. There was a marked improvement in the condition of the tongue and stomatitis, and later a return of appetite to the patient, who had previously been forcibly fed for a considerable period.

Other cases of pellagra reported in the literature appear to have been successfully treated with yeast and foodstuffs rich in the vitamin B complex. The action of vitamin B₁ alone on the nervous symptoms in these cases does not appear to have been determined.

Polyneuritis associated with numerous clinical conditions.

The polyneuritic manifestations of beri-beri, alcoholism and pregnancy, and their satisfactory response to treatment with vitamin B₁ have been dealt with. The polyneurites (believed to be true beri-beri) occurring in the course of dysentery, malaria, diarrhoeal conditions, ankylostomiasis, tuberculosis and other febrile and tropical diseases, have also been mentioned, and their response to treatment noted.

In 1933, Wechsler²⁶⁰ studied a series of cases of polyneuritis associated with chronic alcoholism, gall-bladder disease, anaemia, cancer of the stomach and pregnancy. He observed the avitaminosis common to all his cases. Diets rich in all the vitamins were given, with particular regard to vitamin B; many cures were obtained though the specific effect of any particular factor could not be determined.

Perkins²⁶¹ reported a series of 82 cases of polyneuritis associated with pernicious anaemia (3 cases), malignant disease of the gastro-intestinal tract (5 cases), starvation, chronic alcoholism, Korsakoff's syndrome, "wet brain" and pregnancy. Aetiologically, the association of marked gastro-intestinal disturbance

was striking as evinced by anorexia, nausea, vomiting, diarrhoea; in 58 cases (70%) there was complete achlorrhya. The patients were treated with diets rich in vitamin-containing foods. Vitamin B was prescribed in the form of brewer's yeast. Improvement was marked and rapid except in the Korsakoff's syndrome cases, where treatment was prolonged and improvement slow. Whilst Perkins stressed the importance of vitamin B, and the apparent resemblance of these cases to beri-beri and pellagra, he considered that multiple deficiencies were concerned in the production of the pathological changes.

Vorhaus, Williams and Waterman²⁶² observed the therapeutic response of 100 cases of polyneuritis to the oral administration of crystalline vitamin B₁, in doses of 10 mgms. daily (4000-5000 I.U.). No additional vitamins were added to the previous dietaries. The cases were designated "metabolic", "infectious", "with anaemia", "gestational" and "of unknown origin"; 58% had had polyneuritic symptoms for over three months; 35% for over a year. Of the total number of cases, 44 were rendered symptom-free, 48 were improved but not cured, 8 showed no improvement. They concluded that in the cured cases the polyneuritis was due to vitamin

B₁ deficiency, but in that there was no way of distinguishing these cases clinically from others before treatment was begun, the hypothesis was based purely on the clinical response to the administration of the vitamin. The partial response of 48 cases was thought to be due to the incidence of other vitamin deficiencies, and to the continued toxic effects of the original cause. In the opinion of these authors, much larger doses of vitamin B₁ were necessary than were usually considered adequate. (N.B. In America the daily requirement of vitamin B₁ is considered to be about equivalent to 1 mgm. of the crystalline preparation used in the above cases, i.e. about 400-500 I.U. The equivalent of 4000-5000 I.U. was administered daily, therapeutically.)

In the treatment of the above patients, in addition to neurological improvement, there was marked increase of general tone, and appetite. Of eight cases specially chosen on account of associated constipation and intestinal hypotonia, six were markedly improved without any additional therapy.

Polyneuritis following treatment by Gold Salts.

An interesting case was recently recorded by Lescher²⁶³ of a patient who developed polyneuritis a

few days after completing a short course of myocrisin, administered for rheumatoid arthritis. Nervous complications associated with gold salts are very rare, though this treatment is now commonly used. Certain features of the above case, though not emphasised by the author, are significant in the present discussion. The patient's weight was 5 stones 10 lbs., the tongue was red, glazed and devoid of papillae, and gastric analysis showed the absence of free hydrochloric acid. Gold treatment was stopped, and the patient was given "a generous mixed diet, rich in vitamins, especially vitamin B, with hydrochloric acid before food". Sensory phenomena began to subside in four days, and she was able to walk fairly well by the end of the eighth week. Response was somewhat slow, though she was greatly improved at the end of four months. There was no associated anaemia.

Results of the Parenteral administration of Vitamin B₁.

Ritchie Russell²⁶⁴ reported the first results of the parenteral administration of vitamin B₁ in this country in March 1936. The synthetic preparation (issued by Messrs Hoffmann-la-Roche) was used in a series of cases of prolonged anorexia (in sprue,

pernicious anaemia, rheumatic fever and paralysis agitans), polyneuritis and subacute combined degeneration of the spinal cord. In three of the anorexia cases "the appetite returned to such an extent that it was difficult to satisfy their desire for food". In the polyneuritis cases improvement was dramatic, with rapid "shrinkage" of the area of sensory loss towards the periphery. Russell observed that "the improvement following the treatment was in all these cases so rapid that it seems justifiable to conclude that the nerves which recovered so quickly were suffering from an abnormality of conduction which could be easily reversed by administering the vitamin", and was comparable to the improvement obtained so quickly in paralysis caused experimentally by vitamin B₁ deficiency. It was therefore concluded that "deficiency of vitamin B₁ was an important factor in the causation of the nervous degeneration".

More recently similarly satisfactory results have been reported in the treatment of neuritic affections by parenteral administration of vitamin B₁ by Ruschke²⁶⁵ and Gachtgens²⁶⁶, and von Lobenstein²⁶⁷.

The treatment of Subacute Combined Degeneration of the spinal cord by vitamin B₁.

The actual position of peripheral neuritis in the syndrome of subacute combined degeneration is imperfectly understood. Treatment of polyneuritis can only be discussed pertinently, under the heading of the combined cord condition if it actually figures pathologically in the disease. Secondly, since it may be that liver therapy has constituted both a haemopoietic and vitamin treatment simultaneously, this question too may be discussed. I believe that the following observations are essential to a discussion of the factors in treatment of subacute combined degeneration.

This disease furnishes an outstanding example of the difficulties of interpreting the results of any particular treatment. Its clinical association with pernicious anaemia and achylia gastrica is known. The causal factors which determine the degenerative nervous lesions, however, are unknown, but both haemopoietic and hypothetical neuropoietic factors have been assumed by many authoritative observers. The pathology of the more advanced stages of the disease in the central nervous system is well recognised; following a primary demyelination which apparently commences in the centre

of the white columns, there follows a true degeneration in the posterior and lateral columns which may extend upwards and downwards, and may involve the antero-lateral columns. Eventually almost the whole of the white matter of the cord may be affected. Degenerative changes of varying degree are found in the peripheral nerves. Occasionally the disease in the spinal cord is confined entirely to the posterior columns.

The clinical manifestations are, in consequence of such pathological lesions, variable. They may occur late in association with a severe degree of pernicious anaemia; or the nervous symptoms may be prominent whilst the blood changes are barely recognisable and may, in fact, be the means of drawing attention to the haemopoietic system. The early clinical nervous phenomena may be (and usually are) confined to peripheral sensory disturbances, as in polyneuritis, with flaccidity and loss of deep reflexes; the condition may be characterised by spasticity with increased reflexes throughout (rare); or by spasticity changing to flaccid paralysis later, with loss of deep reflexes. All these clinical phenomena naturally depend on the degree of affection of the peripheral nerves, the posterior and lateral columns, and the peripheral and spinal cord changes combined.

For these reasons the difficulties of interpreting changes in the clinical picture during any particular form of treatment are obvious. The return, or increased force of a knee-jerk in polyneuritis constitutes a good sign; in subacute combined degeneration, whilst such a sign may be favourable, it may indicate increasing degeneration in the lateral columns - the tendency towards increased reflexes is now more than off-setting the tendency towards diminution of the deep reflexes consequent upon affection of the peripheral nerves and/or posterior columns. For the same reasons an apparently normal knee-jerk may be the expression of combined postero-lateral degeneration. Again, a severe degree of peripheral nerve degeneration may, by interrupting the reflex arc, clinically mask the degenerative changes in the spinal cord.

Mills²⁶⁸ described a case characterised clinically by spasticity and exaggerated reflexes; ^{at} autopsy, though there was marked external demyelination of the posterior columns of the cord, there was "little or no evidence of degeneration in the motor tracts". Such observations serve to show that the nervous clinical manifestations may not be a true reflex of the extent and nature of the pathological lesions.

The various criteria used by numerous observers, as indicating improvement in the neurological condition, are diverse; emphasis is variously placed on sensory improvement, vibration sense, return of reflexes, loss of spasticity, increased muscle tone as evidenced by a less degree of flaccidity, improvement in walking power, and so on. Many of these "improvements" may actually have been due to retrogressive changes.

A study of the literature reveals that the earliest changes in the condition which eventually becomes subacute combined degeneration have not been adequately investigated histo-pathologically, particularly in the periphery. Most haematologists are now agreed that in a high percentage of cases of pernicious anaemia signs of degenerative changes in the various components of the nervous system can be discerned during the first attack of the anaemia. Vaughan²⁶⁹ has estimated the incidence to be as high as 92%. For this reason I consider that the most reliable information bearing on early nervous system changes in subacute combined degeneration is to be found in the post-mortem descriptions of pernicious anaemia patients who succumbed before gross signs of the former disease were manifest.

Hamilton and Nixon²⁷⁰ (1921) described a case in

which the only change in the cord was "a possible pallor along the dorsal groove". Vaughan describes the nature of the early pathological process in the cord as a demyelination, resulting in wide, slender rings of myelin; the axis cylinders disappear coincidently with the complete disappearance of the myelin. (This observation is identical with that of Greenfield and Carmichael, previously referred to, on the changes in peripheral nerves.)

Greenfield and O'Flynn,²⁷¹ following post-mortem analysis in pernicious anaemia cases, observed that if death ensues in the early (neurological) stages, only a posterior column degeneration is found. They described a case in which, clinically, sensory symptoms had been present for a year before death, immediately previous to which a Babinski plantar reflex was obtained; at autopsy, degeneration was confined to the posterior columns, and in the lateral columns the only abnormality found consisted of one or two minute "vacuoles" (this patient had had no liver therapy). Agreement with these observations was expressed by Baker, Bordley and Longcope²⁷² in 1932: "In considering the nervous system, it is important to remember that many symptoms and signs are due to peripheral nerve

involvement, rather than, as used to be believed, to spinal cord lesions".

Unfortunately, though pathological descriptions of spinal cord changes are numerous in the literature, the peripheral nerves and their endings have not received the same attention. The minute nature of these changes as described by Greenfield and Carmichael has been noted, and found to be identical with those found in alcoholic neuritis; these and the observations discussed above, lend support to the view that wherever the beginnings of the degenerative lesions in subacute combined degeneration may be, peripheral nerve degeneration is an integral part of the disease and not fortuitous.

The observation that in both the spinal cord and the peripheral nerves the earliest pathological change is to be observed in the protective myelin sheath (as also obtains in other studied forms of polyneuritis), and the fact that the early clinical phenomena and the early pathological findings are referable in most cases to the peripheral nerves and the posterior columns, would seem to justify a re-investigation of the early pathological processes not only in the posterior columns of the cord but in the peripheral nerves and

their terminations in the neuro-muscular apparatus.

With the above reservations regarding our knowledge of subacute combined degeneration, reference may be made to such responses to treatment which have been noted. It may be stated frankly that the major part of such treatment has consisted in the administration of various preparations of liver, and other measures devoted to the cure of the associated anaemia. Where vitamin preparations have been administered, they have been combined with liver therapy, and therefore their value is difficult to assess. Secondly, all such treatment has often been prescribed in the pronounced degenerative stages of the disease when irreversible changes have taken place. Russell Brain²⁷³ recently stated that "though there is evidence that lack of vitamin A and of the B complex may be followed by degenerative changes in the nervous system, these vitamins alone are ineffective in the treatment of subacute combined degeneration". This probably expresses the view generally shared.

There is almost united opinion that the degenerative changes in the nervous system can only be arrested by maintaining the blood at the maximum level in both corpuscles and haemoglobin elements, by liver, and to a

less extent by iron therapy. On the *modus operandi* of this treatment opinions are divided. One group regards any improvement of the nervous symptoms as being due to the effects of an improved circulation, better general health and strength, and re-education and training - and not to any specific effect of the liver factor or to any change in the nervous lesions, which are but arrested. The other group, of whom Ungley and Suzman²⁷⁴ and Farquharson and Graham²⁷⁵ may be cited, believe the arrest of the nervous phenomena to be due to a specific effect of the liver therapy on the nervous system lesions. They consider that such lesions may not only be arrested but may be improved in some cases, with adequate treatment. Thirdly, there are many who have found that liver preparations, to be of service in the treatment of subacute combined degeneration, must be given in much larger doses than those which are adequate in maintaining the blood condition at the 100% maximum. Such observations imply that liver, as used therapeutically, (a) contains some factor beneficial both haemopoietically and neurologically but necessitating larger amounts to effect the latter, or (b) contains some factor (or factors) in addition to the anti-anaemia one, which materially affects the course

of the nervous lesions, but which again requires proportionally larger amounts of liver in order for its effects to be made manifest.

Since so much of our present reasoning in both pernicious anaemia and subacute combined degeneration is based on hypotheses as regards aetiological, causal and pathological factors, and since there is a lack of unanimity in ascribing beneficial results accruing from treatment to any known therapeutic agent, is it not possible that at least some fraction of neurological repair might be due to certain nutritive factors contained in liver? Is there any knowledge to support such an hypothesis?

Ox liver is rich in vitamins A, E, B₁ and B₂. Some commercial liver extracts are rich in vitamins B₁ and B₂ (Vitamins: Survey of present knowledge, Med. Res. Council, 1932, page 311). Fresh ox liver has a vitamin B₁ content of 32 Cowgill mgm.-equivalents per gram: 500 grams of raw liver daily would therefore yield a quantity of vitamin B₁ equivalent to 800 international units, in addition to vitamins A and B₂. (Whilst some commercial liver extracts are deficient in vitamins B₁ and B₂ and contain no vitamin A, many modern oral preparations of liver have supplementary

amounts of vitamins added to them, e.g. Livogen (B.D.H.) contains per fluid ounce the vitamin B equivalent of 4 oz. of fresh yeast. On the other hand (though many preparations have not been assayed) the majority of the concentrated preparations for intramuscular injection are either vitamin deficient or contain none at all.) Campolon (Bayer) contains no vitamin B₁ according to a personal communication from the manufacturers.

It is therefore significant that numerous authoritative observers have stated that whilst marked improvement in the blood condition can be attained by parenterally administered liver, the neurological symptoms apparently respond more satisfactorily when this form of therapy is supplemented by the oral administration of liver extracts or fresh uncooked liver. Koessler and Maurier²⁷⁶ treated a large series of patients suffering from pernicious anaemia and nervous lesions with a high calorie diet and a superabundance of all vitamins; additional supplies of red meat, liver and kidney were given; better results were obtained by these measures than any treatment previously administered by them. Davidson²⁷⁷ observed in 1933 that subacute combined degeneration appeared most frequently in patients who were relying more on prepared

liver and stomach extracts and who took no oral (domestic) liver. Ungley²⁷⁸ observed that the potency of brain tissue in producing an increase of the reticulocytes and red blood cells was only a third that of the liver; but as regards the effect on the nervous system, brain produced a definite neurological improvement in doses which had relatively little effect on blood regeneration compared with liver. Now ox brain contains no vitamin A, is poor in vitamin B₂, but contains good supplies of B₁ - 13 Cowgill mgm.-equiv. per gram; 500 grams therefore contain roughly 312 international units. If brain were prescribed primarily for its haemopoietic effect (i.e. according to Ungley, in treble the quantity as compared with liver), then the patient would be receiving the equivalent amount of anti-anaemic substance as in liver, but over 100 international units of the antineuritic factor more, per day, in addition to vitamin B₂. Against this it may be argued that since much evidence has been quoted indicating (though not proving) that gastro-intestinal disturbances predispose to malabsorption of food factors, any vitamins contained in liver or brain might suffer this fate; and in consequence any beneficial effects on the nervous system would probably not be due to any oral administration

of such substances in a disease consistently characterised by achylia gastrica.

Against this it may be argued that, because of malabsorption, many cases may have failed to respond to oral therapy on account of insufficient dosage of liver; or through the administering of liver extracts which, while rich in anti-anaemic factor, were deficient in vitamins. The virtue of the anti-anaemic substance contained in liver lies surely in the fact that it is the combined product of the "intrinsic" and "extrinsic factors" as found in a healthy stomach - not an achlorrhidric one; it therefore supplies what the achylic stomach of pernicious anaemia cannot create, and to that extent the anti-anaemic factor stored in liver tissue is independent of gastric dysfunction; it may be regarded as a pre-digested substance.

On the other hand, the other nutritive factors contained in liver, such as vitamin B, do not (as far as is known) differ in composition from the same factors contained in other foodstuffs. Vitamin B is, therefore, subject to the same destructive and malabsorptive influences consequent upon achlorrhidria and gastrointestinal derangements, whether given in the form of liver or any other food or preparation. In this

connection one must regard as significant Vaughan's observation: "Vitamin B₁, with rare exceptions, is useless in treating the cord lesions of pernicious anaemia, but (quoting Gildea, Kattwinkel and Castle) it is extremely satisfactory in cord lesions produced experimentally in dogs by vitamin B deficient diets but with normal gastric secretion."²⁷⁹

The vitamin deficiency hypothesis as a contributory factor in the nervous lesions of pernicious anaemia may be viewed from another standpoint. The two outstanding clinical conditions associated with vitamin B complex deficiencies (disregarding for a moment individual factors) are beri-beri and pellagra. Both are associated with degenerative conditions of the peripheral nerves and the spinal cord. In beri-beri the nervous condition is predominantly polyneuritis with lesser degrees of spinal cord involvement; in pellagra the commonest complicating nervous lesions are Korsakoff's syndrome and subacute combined degeneration of the spinal cord. The only other recognised clinical condition with which subacute combined degeneration is commonly associated is pernicious anaemia. Is it not therefore conceivable that the same factors might operate in the nervous lesions of pernicious anaemia as

are known to operate in beri-beri and pellagra - vitamin B? In the latter conditions the aetiological factor is a dietary deficiency. In pernicious anaemia might not the deficiency be in part truly dietary owing to anorexia, and partly a conditioned-deficiency of malabsorption owing to the invariably accompanying gastro-intestinal derangement and achlorrhya?

In conclusion, whether the hypothesis outlined here is near the truth or not, the fact remains that the oral administration in the past of raw and partially cooked liver, and those liver extracts known to be rich in the vitamin B complex, has constituted not only a haemopoietic therapeutic measure of proved value in blood regeneration, but (and possibly inadvertently) a form of vitamin B therapy, the neurological value of which is, as yet, a matter of conjecture and personal opinion. If vitamin B₁ plays any part in the nervous lesions of subacute combined degeneration, it is in the peripheral nerve manifestations that one would look for improvement. Greenfield and O'Flynn²⁸⁰ in reviewing their results of liver therapy in subacute combined degeneration, observe that much of the accruing benefit is "probably due to the improvement of a peripheral neuritis", and that the effects of liver may be due to

arrest of the degenerative process before the lateral columns in the cord are attacked. Davidson, McCrie and Gulland²⁸¹ concluded that nervous symptoms (in pernicious anaemia) if recent and in the nature of paraesthesia may, with adequate liver treatment, completely disappear; but no cure could be expected if actual destruction of nerve-tissue had occurred.

Ritchie Russell²⁸² observed the effects of parenterally administered vitamin B₁ in cases of subacute combined degeneration: "In these cases also the giving of the vitamin was quickly followed by shrinkage towards the periphery of the area of sensory loss."

The further investigation of the treatment of cases of subacute combined degeneration or, more aptly, of the early nervous lesions in pernicious anaemia, should be fraught with much interest. The therapeutic response of such cases to the administration of vitamin B₁ by the parenteral route should help to elucidate the extent to which this factor is involved in the aetiology of this nervous syndrome.

INVESTIGATION OF CASES OF POLYNEURITIS.

In the investigation and treatment of the following cases, an attempt was made as far as possible to confine attention, both aetiologically and therapeutically to vitamin B₁. No other vitamin preparations were used to supplement treatment apart from those in ordinary diets.

Detailed dietary values were calculated only in those cases where accurate details over a prolonged period could be supplied, and/or where border-line values of vitamin B₁ were thought to exist which might be correlated with Cowgill's predicted requirement. In the assessing of calorie and vitamin B₁ values of such diets I received great assistance and guidance from the staff of the Royal Infirmary Dietetic Department. The vitamin indices for the various foodstuffs in the diets calculated, were taken from Cowgill's "Vitamin B₁ requirement of Man" to which reference has been made; a list of vitamin B₁ values for common foods has been included in this thesis. (See p. 146.)

Until the major part of this investigation had been completed, the estimation of blood bisulphite binding substances was not seriously considered. In

addition it constitutes a by no means "every day" biochemical test of some delicacy. Dr C. P. Stewart and his staff, however, very kindly carried out a series of estimations in four cases. The significance of the results cannot be appreciated until much further investigation has been made; but they at least showed a definite consistency in response to vitamin B₁ and it is regretted that the same procedure was not employed with the cases studied earlier.

The bisulphite binding substances were determined by the method of Clift and Cook, as described by Platt and Lu²⁸³ and are expressed as mg. pyruvic acid per 100 Grm. blood; 1 c.c. N/100 l = 0.44 mg. pyruvic acid.

Fractional gastric analysis was made whenever possible; some of the cases were seen and treated as out-patients, and in one or two cases gastric analysis was not possible.

Dr Ritchie Russell has kindly placed at my disposal the reports of the first five cases treated by him by parenteral vitamin B₁ injection; these are included in the following series.

CASE RECORDS.

(Cases 1 to 5 - Dr Ritchie Russell)

Case 1. Chronic Progressive Polyneuritis.

A married woman, aged 44, was in fairly good health until the end of August 1935, when, while in London, she had a violent attack of diarrhoea and vomiting which lasted for a day. The day following she noticed a feeling of pins and needles and numbness in the tips of the fingers, in the feet and in the calves of the legs. The parts affected with the tingling then began to feel increasingly cold and somewhat painful. The numbness and tingling gradually spread to involve the back, tongue, lips and the point of the nose, and at the same time began gradually to spread up the extremities from the periphery. Early in September the patient came to Scotland and began to notice weakness of the limbs. When examined on 24th September 1935, she had great difficulty in getting upstairs. There was well-marked peripheral sensory loss extending to the wrists and above the ankles. The muscles were extremely tender and the tendon reflexes were all absent. She was admitted to a nursing home, but the condition continued to become gradually worse. Examination of the other systems showed no gross abnormality. The blood count was normal except that there was a relative increase of lymphocytes which formed 40 per cent. of the differential blood count: the Wassermann reaction was negative. There was no evidence of poisoning with alcohol or arsenic. The weakness gradually progressed in spite of various forms of treatment that were tried. Injections of strychnine hydrochloride, gr. 1/30 once daily, were followed by pain and a feeling of swelling in the hands and feet after each injection; and during the week in which this treatment was tried the paresis continued to increase. The administration of thyroid, gr. 1 twice a day for a week, seemed to hasten the progress of the disease. Injections of campolon and the giving of marmite, halibut liver oil, and orange juice by the mouth failed to arrest the progress of the disease. Hot-air baths had no good effect. For two weeks the patient was given daily intramuscular injections of calcium gluconate, but during this period also she became worse.

For another week she was given 5 units of parathormone each day, at the same time taking 120 grs. of calcium lactate by the mouth daily. By 10th December 1935 she had become very helpless. The hands and feet were almost completely paralysed and the proximal muscles were also weak. She had difficulty in holding up her head and in turning in bed. Considerable sensory loss had spread over the whole body and there was marked loss of all forms of sensation over the extremities, extending up to the shoulders and hips. On 10th December 1935, following an attack of coughing, the patient became very breathless, the heart became very rapid and feeble, and profound collapse ensued. There was a great feeling of tightness in the chest, the left side of the heart became dilated and there were tetanic spasms in the hands and feet. An injection of parathormone appeared to relieve this attack, but the blood calcium content was found to be normal. Another similar attack developed two days later.

On 12th December 1935, 100 international units of vitamin B₁ (B.D.H.) were given subcutaneously. Two days later some improvement in the appreciation of pin-prick was noticed for the first time below the shoulders on both sides. Injections of vitamin B₁ were repeated every third day, and by 20th December 1935 appreciation of sensation had returned to both the upper arms and the thighs. The patient said she was able to feel the temperature of hot water on her face and body for the first time for several weeks, while the numbness of the tongue and nose had become much less. The patient reported that her whole body felt much warmer since the injections were started.

Examination of the stools revealed the presence of cysts of Entamoeba histolytica, which had presumably been present since an attack of dysentery twenty years previously.

On 26th December 1935 (two weeks after the first vitamin injection) the patient could appreciate pin-prick over the whole of both lower extremities and down to the wrists in both upper extremities. The injections were continued regularly, and a week later she could appreciate pin-prick on all her fingers and toes and there was a great return of power in the proximal muscles. By the middle of January 1936 she

was able to sit up in a chair and could move much more freely, but her progress was delayed by great pain, with some swelling, in both hands. Some power of dorsiflexion of both feet had by now returned on both sides and the sensory loss had disappeared entirely from the nose and tongue. The improvement continued, and by the end of January the right biceps-jerk was found to have returned. After commencement of the treatment with the vitamin there were no further heart attacks and the position of the apex of the heart, which was outside the nipple line during the attack in December, returned to a position half an inch internal to the nipple.

On 12th February 1936 the appreciation of small passive movements of the fingers and toes was found to be normal for the first time. The biceps-jerk was also present for the first time on the left side. By the end of February the strength of her legs and trunk had improved greatly and the patient could take a few steps with a little support. Slight contracture of the tendo achillis caused pain on attempting to walk. The arms were strong, but the hands were still swollen and painful. The vitamin injections were at this time being given at intervals of about twelve days. A sensation of "pins and needles" at the tips of the fingers developed about ten days after each of the last three injections, but disappeared in six to ten hours after a further injection. The patient stated that the feeling of "pins and needles" was the same as that experienced at the beginning of the illness. This sensation developed in spite of the fact that the patient had been taking one or two teaspoonfuls of marmite daily for four weeks.

Case 2. Alcoholic Neuritis.

A male, aged 34 years, was admitted to Chalmers Hospital on 2nd March 1936 complaining of pain and stiffness in the legs which had been present for the past four months. Two years ago the patient was treated in the Royal Infirmary, when he was found to be suffering from alcoholic neuritis. There was at that time weakness in walking and a numb feeling in the legs, up to the knees, on both sides, and also

tingling in the tips of the fingers. He had previously been taking about a bottle and a half of whisky a day for two years. He was treated in hospital for five weeks and his condition improved greatly, though a numb feeling in his feet has persisted ever since. About a year ago he started taking whisky again to the same extent. During the past four months he has been unable to take much food, and during this period weakness of the legs has become much worse, as also has the numbness in the fingers. On examination the lower extremities were slightly atrophied, tendon reflexes were absent and the muscles were very tender. There was impairment of cutaneous sensibility distal to a level three inches above the knees on both sides. There was also some sensory loss over the fingers. The dorsiflexors of the feet were very weak and could be overcome by the pressure of the examiner's little finger. On the day after admission, treatment by injection of vitamin B₁ (Hoffmann-La-Roche) was started, 800 units being given on the first day and 400 being then given daily for a week. Thereafter an injection was given every third day. On the day after the first injection the upper level of sensory loss in the legs was found to be three inches lower than on the day before. This improvement continued steadily and, within ten days of the treatment being started, normal sensation had returned to the fingers, to the knees, and to most of the leg. The walking had improved greatly and no more cramp was complained of. The patient could now walk a measured distance in 23 seconds, whereas a week previously he required 34 seconds for the same distance. Walking no farther than the length of the Ward caused cramp in the legs on admission, but he could now walk ten times the distance without any cramp occurring. On 25th March the knee-jerks were found to have returned.

Subacute Combined Degeneration of the Spinal Cord.

Case 3. A married woman, aged 46 years, was treated for pernicious anaemia in 1932. At that time her legs were weak and they have remained weak ever since. In November 1935 she had an attack of influenza and since

then walking has been very difficult and unsteady. The patient was admitted to Dr Hewat's Ward of the Royal Infirmary of Edinburgh on 9th January 1936. The red blood cell count was 1,920,000 per c.mm., and the colour index was 1.2. Treatment with parenteral liver extract was followed by a reticulocyte count of 20 per cent., and by 29th January 1936 the red cell count had become 3,480,000 per c.mm. On 30th January 1936 it was found necessary to discharge the patient, her treatment to be continued as an out-patient. Walking had not improved while she was in hospital.

She was not seen again till 27th February 1936, when she reported that her walking was as bad as ever. She had received no treatment since leaving hospital. The gait was spastic and ataxic. The knee-jerks were brisk, the ankle-jerks were absent, and there was a bilateral extensor plantar response. There was marked loss of position sense in both lower extremities. In addition, there was a subjective feeling of numbness in the lower extremities which extended to above the knees. Analgesia to pin-prick was present over both lower extremities distal to a level just above the knee. Over the same area light touch was not appreciated.

On 27th February 1936 the patient was given, as an out-patient, 800 international units of vitamin B₁ (Hoffmann-La-Roche) intramuscularly. When she reported four days later, she said that there was no improvement in her legs. Examination, however, showed shrinkage of the area of sensory loss to a level of two inches below the patella. 800 units were again given, and when the patient was next seen on 6th March 1936 she stated that on the evening of the last injection she found that her walking had become steadier. She was now able to walk better than for four months. Sensation was found to be normal to a level five inches distal to the knees.

A further injection of 800 units was given on 6th March 1936, and on 10th March cutaneous sensation was found to be normal proximal to the ankles of both extremities. On 13th March 1936 cutaneous sensation was found to be normal over both legs and the dorsum of both feet. Walking was now quite steady with slight support to one arm. Numbness, however, was still

present on the soles of the feet and toes, and position sense in the feet was still grossly impaired.

Case 4. A male, aged 64 years, had suffered from symptoms of advanced subacute combined degeneration of the spinal cord and pernicious anaemia for three years when he was admitted to Dr Hewat's ward in the Royal Infirmary of Edinburgh in January 1936. The lower extremities showed marked pyramidal rigidity which caused him considerable pain. There was gross loss of position and vibration sense, but little sensory loss to pinprick or light touch. The red blood cells numbered 4,100,000 per c.mm. and the colour index was 1.1. There was complete achlorhydria.

After a period of two weeks' observation in hospital without any treatment being given, 400 international units of vitamin B₁ (Hoffmann-La Roche) were given subcutaneously. The patient, who is an excellent and matter-of-fact witness, stated that on the evening of the day on which he received the first injection he felt a warm feeling in his lower extremities, and on the following morning was surprised to find that he could move them better than for nearly a year. They were less spastic and consequently less painful. The legs felt more natural and there was no longer an unpleasant sensation when they touched each other. He was able to walk better than had been possible for over a year, and while sitting was able to cross his legs without having to lift up one knee, for the first time for over eight months.

As there was no sensory loss in the fingers, or other sign of peripheral nerve degeneration, I had grudged using the vitamin for this case, as the spinal cord degeneration appeared to have reached an irreversible stage. The patient was given marmite and injections of liver extract, and the improvement in walking was well maintained when he was examined on 5th March 1936.

Case 5. A married woman, aged 55, was examined on 4th January 1936. She complained of numbness in the legs and fingers which had been present for three months. Knee- and ankle-jerks were absent and there was loss of vibration sense over both lower extremities. The plantar reflexes were flexor in type. There was impairment of the appreciation of light touch, and pain over both legs and extending to above the knees on both sides. Appreciation of light touch was also impaired over the fingers of both hands. A subjective sensation of tingling was felt over both hands up to the wrists and over both feet to above the ankle. The red blood cells were 3,100,000 per c.mm., and the colour index 1.1. Daily injections of 2 c.c. of campolon were given for ten days. The blood picture improved, but the sensory disturbances in the hands and feet showed no change. The patient was then given daily injections of 400 units of vitamin B₁ (Hoffmann-La Roche) for three days. On the third day she noticed less tingling in the fingers, and within a week of the first vitamin injection the sensory disturbances disappeared from her hands, except for a slight numbness at the tips of the fingers; the legs also improved greatly, a slight numbness being now present only up to the ankle, and the tingling sensation being present only in the soles of the feet. Liver injections were then resumed and the clinical condition continued to improve slowly. The red blood cell count was 4,500,000 per c.mm. on 15th February 1936.

Case 6, a male, aged 63, employed as a roadman, was admitted to Ward 32 on September 3rd, 1936.

He complained of pains in the stomach of three to four months' duration, which were not severe but constant. Meals produced a feeling of distension and fulness in the stomach which were relieved by bringing up large quantities of wind. He was a chronic sufferer from constipation, and occasionally vomited watery fluid before breakfast. There was almost complete loss of appetite, with nausea at the sight of food. There had been a loss of weight of two stones in three months.

Habits.- Takes no alcohol: light smoker. Without laxatives, the bowels move about once a week.

The patient was sent by his doctor for investigation of the gastro-intestinal tract - malignant disease being suspected.

X-rays revealed no signs of malignant or organic disease of stomach or bowel. There was definite hypotonia of gastro-intestinal tract.

Gastric analysis showed complete absence of free HCl (achlorhydria). The total acidity was 4, 4, 5, 4, 4 in half-hourly fractions.

Tests for blood in the stool were entirely negative.

Interest in this case arose from fact that this patient had certain features already noted in many polyneuritics - a low diet deficient in all elements, including vitamin B₁, anorexia, chronic constipation, hypotonic condition of the bowel, achlorhydria with a smooth, glazed tongue. Although advancing no complaint of peripheral neuritis, he was examined with a view to determining whether any signs or symptoms were present. He complained only of tiredness in the limbs, and "sleepiness" of feet not amounting to true numbness. At times, particularly after resting, there was a suggestion of "pins and needles" in the feet but nothing more. No muscle cramps were complained of but there was slightly more tenderness than normal on deep pressure over the calves. No sensory loss could be detected. There was a flexor plantar response, and the knee and ankle jerks were not easily elicitable, even

by re-inforcement.

The conclusion reached was that there was a suspicion of the presence of symptoms suggestive of early polyneuritis which might tend to progress to the more definite clinical picture if untreated.

That there seemed to be a vitamin B₁ deficiency factor in his case was evidenced by administering parenteral B₁, 400 international units daily. The appetite quickly responded, he was able to take a more generous diet, there was a slight improvement in the constipation on his discharge from hospital after four weeks, during which time he had gained 7 lbs. in weight. He admitted that his feet and legs felt less "wooden", though the possibility of polyneuritis was not suggested too strongly to him for psychological reasons. The deep tendon reflexes in the legs, sluggish on admission, were brisker on discharge.

The patient was not given ac. hydrochlor. dil. with meals until after the return of a normal appetite.

A repetition of the test meal after four weeks showed no alteration in either free or total acidity. (Some observers have noted increase in gastric acidity in experimental animals, or at least a return to normal following the hypo- or anacidity produced during avitaminosis.)

Case 7 . Polyneuritis associated with dietetic deficiencies.

A female patient, aged 52, was consulted as an out-patient in the Edinburgh Royal Infirmary on October 1st, 1936. She had no settled occupation, was a spinster, lived mostly alone and was occasionally employed as a housekeeper-companion.

She complained of "pins and needles" sensations, tingling and pricking pains in the finger tips and hands; loss of sensitivity was causing increasing inability to use her fingers in sewing and domestic work, and she was habitually "letting things fall". After retiring to bed, the fingers began to burn and moderate insomnia had resulted. On questioning, she had begun to suffer a few years previously from "cold fingers" and degrees of numbness, lasting from a few hours to a few days. These sensations occurred only during the winter months and were never present in the summer. During the past two winters, however, the condition has changed to a tingling nature as previously described but had passed off. During the early summer of 1936 the present symptoms had arisen, and various drug and tonic treatments had effected no improvement.

There was a long history of dyspepsia, chronic constipation, fulness and often pain after meals and regular attacks of flatulence. The appetite was poor and she was getting to hate the sight of food; for the past few months she had eaten very little. The diet consisted mostly of cups of tea or weak coffee, toast, bread and butter, scones, fish, kippers and jam. She was unable to eat raw or cooked fruit, potatoes, vegetables or meat on account of the inevitable indigestion these foods caused. She was not fond of milk and only seldom ate a boiled egg. She had at times a craving for "acids" such as vinegar, and liked foods with which the latter could be taken, such as shellfish. Owing to the capriciousness of the appetite, and marked variations in the diet, both quantitatively and qualitatively, no attempt was made to calculate calorie or vitamin values. The diet was obviously deficient in all essential factors..

In the family history, there was said to be a tendency to gout, and both parents had always had

stomach trouble. The patient had never taken alcohol and was a non-smoker. There was an absence of symptoms in the lower limbs.

The patient was stout, pale and flabby, with general lack of muscular tone. The hand-grip was weak, and the hands tender when squeezed. There was anaesthesia to light touch and pin-prick in the fingertips and impaired cutaneous sensibility proximal to the wrist. The supinator jerks were absent, and the biceps and triceps elicitable with difficulty. Knee and ankle jerks were sluggish, there was no discernible sensory loss in the lower limbs and the plantar reflex was flexor.

Mentally the patient was dull, lacking in concentration and a poor co-operator. The tongue was large, pale, flabby and moist, and there was papillary atrophy at the margins. Cascara was prescribed as a laxative, and ac. hydrochlor, dil. in one dram doses diluted in orange juice twice daily with food.

The patient promised to take regular meals consisting of eggs, milk foods, Bemax, oatcake, fruit juices, vegetable purées, lean meat and marmite, in soups or on toast. During the first week, 3 injections of vitamin B₁, 400 units (Hoffman-la-Roche) were administered. By this time, the fingers felt warmer and more comfortable, with "pins and needles" persisting in the tips. During the following two weeks four more injections were given at three and four day intervals. The area of sensory loss had left the wrists and hands; occasional tingling sensations were felt in the tips of the fingers, but she was now able to thread a fine needle and sewing could be more easily accomplished. It was found possible to admit the patient to hospital for a day, for Gastric analysis; there was complete absence of free hydrochloric acid and the highest total acidity reading in six fractions was 6; there was an almost complete absence of mucus. Two more weekly vitamin B₁ injections were given, after which they were discontinued. The supinator jerk had not returned.

Comment. This localised form of polyneuritis appeared to be due to dietetic deficiencies both absolute and conditioned by manifestations suggestive of atrophic gastritis and poor assimilation. The

response to vitamin B₁ indicated that a defect of this nature was implicated, and the possibility that such a deficiency may itself have contributed to the prolonged anorexia and diminished gastric secretion is conceivable. In addition, a circulatory-gouty tendency was suggested by the family history and attacks of "cold fingers", and may have functioned in localising the polyneuritis to the fingers. The occurrence of previous attacks in the winter months only is in keeping with the prevalence of dietary deficiencies at these periods.

Case 8. Polyneuritis associated with dietetic deficiencies.

A roadman, aged 54, was admitted to Ward 22 in the Royal Infirmary on November 26, 1936. Two to three months before admission he had felt "pins and needles" sensations, and tingling in the fingers which had gradually spread up the arms to above the elbows. The feet were similarly affected shortly after the fingers, and felt alternately numb and cold, and tingling and hot; these sensations had gradually involved the limbs up to the thighs, and then ~~on to~~ the skin of the lower abdomen by the time he was admitted to hospital. Seven weeks before admission he had suffered from "gastritis", with vomiting, diarrhoea, nausea and flatulence, and stayed away from work for two weeks. Sensory symptoms had not worried him much until that time, but after being back at work for a week, they became more noticeable, and it was from then onwards that they spread up the limbs more rapidly and more uncomfortably. His boots began to feel tight and although he continued his work, he always felt tired. His appetite had been fairly good but variable lately. He had had influenza five years earlier, but otherwise had been healthy until the present nervous and gastric symptoms had appeared. Apart from occasional "fulness" and flatulence after occasional meals, he did not suffer from indigestion. His walking had not been impaired by the present complaint, apart from tiredness in the legs, and a numb feeling in the soles of the feet. No neuralgic pains or cramps were complained of. There was a "peculiar numb feeling" in the palms of the hands when using his roadwork tools.

On examination, the pulse was 80, systolic blood pressure 140, the diastolic 86. The tongue was moist, slightly furred, and showed no sign of papillary atrophy. Heart and lungs were healthy, and there were no urinary abnormalities. The cranial nerves were normal and Wassermann reaction negative. Blood - R.B.C. 4,400,000, Haemoglobin 88%; W.B.C. 7,800.

There was impaired cutaneous sensibility to pin-prick and light touch from the toes to the knees, and very slight patchy impairment in the distal third of the thigh. The fingers, palms and backs of the hands were almost anaesthetic to light touch, with less

marked impairment up to the elbows. Simple objects placed in the palms could not be recognised by touch. The calf-muscles were slightly tender on pressure; muscle-tone was good and limb movements well performed; there was no ataxia, and no foot or wrist drop. Hand grip was good on both sides, and the gait was steady. There was no Rombergism. The disturbances were therefore almost entirely sensory. The biceps and supinator jerks were absent, the triceps jerk weak and sluggish. The knee-jerks and right ankle jerk were diminished, the left ankle-jerk absent. The plantar response was flexor.

Diet before admission - subsisted on with little variation for at least a year. Breakfast: usually bacon and one egg, scones, white bread with "grease" or margarine, coffee. At 9 am. - coffee, scones, grease (used as butter), jam. At noon - coffee, scones or white bread, with jam; occasionally potted meat sandwiches. At 5 p.m. - soup (usually potato, with added leeks, carrots or cabbage), stew, or potatoes; bread or scones; occasionally a milk-pudding.

Vitamin B₁ foods are noticeably deficient in this diet - no cereals and minimum of eggs, milk, red meat, vegetables; abundance of bread, scones and starchy food.

Alcohol - usually three glasses of beer - was taken on Saturdays.

The average daily calorie value of the above diet is (approx.) 2100. The maximum vitamin B₁ content, allowing a liberal quantity of bacon and two eggs per day, and 400 c.c. of milk, is 3556 Cowgill mgm.-equivalents (the minimum value is about 3000 mgm. eq.). The vitamin/calorie ratio is therefore 1.7, and the patient's weight was 64 kilograms. Reference to Cowgill's chart shows that for this weight a VIT/CAL ratio of 1.8 is required, and 1.7 is slightly below the minimum border-line level. Over a prolonged period this diet, according to Cowgill's prediction formula, was therefore slightly inadequate in vitamin B₁.

Gastric function. Fractional test meal showed normal levels of free and total acidity.

The patient was given a diet adequate in all

respects, with quantities of milk, vegetables, fruit, meat and cereals. He was given additional vitamin B₁ in the form of Marmite (2 to 4 drams daily) and 50 I.U. of parenteral vitamin B₁ (Vibex), daily.

Recovery was gradual and maintained, but very slow. There was a gradual shrinkage of the areas of sensory loss from the elbows to the wrists, and from the thighs to the ankles. On January 25th, 1935, there was still slight numbness in the tips of the fingers, and in the toes and soles of the feet. All the deep tendon reflexes were present, the biceps, supinator and left ankle-jerk having returned. Though he admitted to a "velvety" feeling in the palms of the hands, he was now able to recognise objects placed in them.

(Note: I was unable, through temporary absence, to re-examine this patient after January 25, 1937, but I am informed the improvement was maintained and he was discharged from hospital well.)

Comment.-

Whilst the above patient's diet was not grossly inadequate with respect to vitamin B₁, it was borderline for a prolonged period. It is significant that although there were slight sensory disturbances for a short period, these were markedly and rapidly aggravated following the attack of gastritis, with concomitant vomiting and diarrhoea. That this disturbance precipitated a temporary state of gross vitamin B₁ inadequacy, following a prolonged partial deficiency, is conceivable, and is suggested by the subsequent history.

Judged purely by gastric secretory activity, there was no evidence of malabsorption; at the same time a more rapid response to the vitamin may have been obtained by larger parenteral doses.

The clinical phenomena here were almost entirely sensory, commencing in the periphery, and there were no signs indicating spinal cord involvement.

No factors, other than dietary ones, could be discerned, to explain the occurrence of polyneuritis in this patient with a previous history of sound health.

Case 9.

A married female patient, aged 34, was admitted to Ward 33 in the Royal Infirmary on February 6th, 1937. Her principal complaints were a severe cough, breathlessness, palpitation and increasing weakness. She was found on first examination to have a catarrhal bronchitis and cardiac enlargement, with mitral incompetence. Her general appearance suggested a state of gross under-nutrition; though her weight was 8 stones, she was pale, sallow, weary and obviously anaemic. She had had six children in nine years; the last child was born two years ago, and she had never felt really well since.

She gave a full, symptomatic history referable to her cardiac and pulmonary condition, but complained only of tiredness in the legs and "sleepiness" in the feet. This was amplified into numbness and tingling sensations in the toes and ankles on closer questioning. No cramps or pains were complained of; there had been numbness and "pins and needles" in the finger-tips for a month. Distension, discomfort and flatulence were present after food; the appetite was very poor, and had been worse during the past few months. Poverty played a major part in table economies. The tongue was pale, flabby and smooth, and the teeth broken and carious. Gastric analysis showed a total absence of free acid and there was a maximum total acidity of 12.

There was no enlargement of liver or spleen.

Blood examination showed R.B.C. 2,920,000; haemoglobin 35%, colour index .6, white blood cells 6,400. Stained film showed marked microcytosis. Blood Wassermann gave a negative reaction.

Sputum examination revealed no Tubercle Bacilli. The urine was acid; there was a faint trace of albumen and a deposit of phosphates.

The cranial nerves were normal, the pupils were equal, regular and the reflexes normal. Muscle tone was very poor, and there was marked general flabbiness. There was abnormal tenderness on pressure of the calf-muscles. Analgesia to pin-prick and light touch was

found in the toes, the dorsum of the feet and extended to a level about three inches distal to the knees. Impaired sensation in the hands was confined to the fingers. The triceps, biceps and supinator, and knee- and ankle-jerks were all absent; difficulty was met in eliciting the plantar response owing to hyperaesthesia of the sole of the foot, but was found later to be flexor.

The maximum daily diet for the last two or three months had consisted of toast, tea, biscuits, white bread with either butter or margarine, potatoes, meat infrequently, about twice a week in the form of mince, and milk only with beverages and an occasional milk pudding. Cereals, eggs, vegetables and fruit were conspicuously absent. A detailed list of foodstuffs as described by the patient and in the quantities stated, was made and its values assessed at the Dietetic Department, as follows: Milk 400g; potatoes 60 g; white bread and biscuits 60 g; butter 20 g.; meat 60 g; this daily diet has a calorie value of 1050, and a vitamin B₁ content of 1636 Cowgill mgm.-eq. The VIT/CAL ratio is therefore 1.56, and therefore adequate in vitamin B₁ content according to Cowgill's predicted requirement for a body weight of 55 kilograms. The patient's weight was 51 kilograms. If her symptoms were in any way referable to a vitamin B₁ deficiency, she was developing the former on a diet supposedly adequate.

The patient was kept in bed and given a light, rich diet of milk, eggs, rabbit, fruit-juices, chicken and fish. The appetite was poor, much of the food not partaken of and not enjoyed.

On the fifth, sixth and seventh days in hospital, 1000 international units of vitamin B₁ ("Betaxin") were injected simultaneously. Afterwards 500 I.U. were given daily. On the fourth day the patient was brighter, admitted to feeling much better and there was marked improvement in appetite. She said she could "taste her food better". This was maintained and the diet was accordingly increased, red meat, potatoes, vegetables and cereals being added; acid hydrochlor. dil. was given twice daily with food and little flatulence or discomfort was complained of. At the end of the first week, the numbness and "pins and needles" had gone from the fingers and the feet

merely felt sleepy. Iron was given now in the form of Ferri et ammon. cit. gr.xxx t.i.d. At the end of the second week cutaneous sensibility had returned in the feet, the tips of the toes showing slight analgesia. There was no return of any of the deep reflexes. Pressure over the calf-muscles was still tender.

At the end of the third week the patient was greatly improved; the pulse was 76, the cough had gone. Blood examination showed increase in R.B.C. to 3,900,000 and haemoglobin to 70%. She was taking more food than for years and enjoying it for the first time. Before discharge she had her carious teeth removed. She was advised to go to Convalescent Home for a brief period, in order to continue her treatment and to have the blood condition restored to normal but she decided against it. Examination before discharge revealed normal sensation in the feet; the calf-muscles were slightly more tender than normal. None of the deep reflexes had returned.

Bisulphite binding substances were estimated before and during parenteral vitamin B₁ treatment and were as follows:-

Date	Vit. B ₁ Parenterally	B.B.S. (Blood)
	("Betaxin")	
Feby. 9th		2.77
" 10th		2.87
" 11th	1000 Int. units	
" 12th	1000 " "	2.40
" 13th	1000 " "	2.35
" 14th	500 " "	
" 15th	500 " "	
" 16th	500 " "	2.01

There was thus a drop of 0.76 in bisulphite binding substances following the administration of 4000 units of vitamin B₁.

Comments.- The nervous symptoms appeared to be associated with idiopathic hypochromic anaemia, in turn associated with rapid childbirths, under-nutrition and achlorhydria. Nervous symptoms are not voluntarily complained of, which perhaps stresses the importance of "suspecting" cases of obvious dietary inadequacy of having peripheral nervous manifestations. The sensory phenomena were not merely circulatory; the symptoms were susceptible of this explanation but not the analgesia of "stocking" distribution, and the absent reflexes. Provided the diet as described to us, and ensuing calculations are correct, this patient had early polyneuritis on a diet, which though poor, was adequate in vitamin B₁ according to Cowgill's prediction. On the other hand the achlorhydria may have been preventing absorption of vitamins comparable to malabsorption of iron and minerals. The response to vitamin B₁ was striking, particularly in influencing the appetite; there was also shrinkage of the area of sensory loss in the lower limbs before any material improvement in the blood condition had occurred. These responses indicate the association of B₁ avitaminosis. The first two blood B.B.S. estimations gave levels within the normal limits as described by workers on this subject; yet there was a marked and maintained drop following vitamin B₁, similar, though of less degree to that in beri-beri, and associated with clinical improvement.

Case 10. Polyneuritis suggestive of Beri-beri.

A male patient, aged 43, was admitted on August 11th, 1936, to Ward 32 in the Royal Infirmary.

He had suffered continuously from gastric catarrh for ten or twelve years, and had had intermittent courses of medical treatment from his own doctor. There had been attacks of irregular vomiting of bile-stained material after meals, sometimes by night. He had been a marine-engineer at sea until six years ago, but had to relinquish his post owing to frequent vomiting attacks and gastritis. Whilst at sea, he frequently suffered from swelling of the fingers and backs of hands, often lasting for a few days; at these times the hands felt numb, were bluish-pink in colour, and queer sensations, as if cold water were trickling over them, were experienced. Rubbing and massage and warmth seemed to help the condition. The ship's diet consisted of eggs, bacon, meat, white bread, fish, margarine, puddings, fruit and vegetables. He was always better on land (at home) than at sea but was seldom free from indigestion and other symptoms of "gastritis". The appetite was capricious; he was always constipated but had occasional attacks of diarrhoea.

The patient was a heavy whisky drinker until twelve years ago, when he was advised to give it up on account of stomach trouble; he has been teetotal since. He is a non-smoker. Chief among his previous illnesses were Enteric Fever in 1915, and Malaria in 1916.

Present History.- Four weeks prior to admission, after a few days of "biliousness" and loss of appetite, he felt very sick whilst taking a walk after breakfast and, following a severe attack of vomiting, he collapsed and had to be assisted home. Three days afterwards numbness and tingling sensations commenced in the feet and gradually extended to the knees, whilst he was kept awake at night by painful cramps in the calf-muscles, as if they were tightly bound. At the end of a week he was only able to walk a few steps about the house, and the act was accompanied by palpitation and shortness of breath. A period of rest in bed effected no improvement, and on getting up, walking consisted of a "shuffle"; he was able to lift the toes from the ground with difficulty, and eventually

they were dragged along. The fingers, hands and arms had in the meantime developed numbness and pins and needles sensations up to the elbows, and there was now added pronounced general weakness, and swelling of the feet and ankles, with almost persistent muscle cramps. Walking had become almost impossible owing to the bilateral drop-foot, and in this condition he was admitted to hospital.

On examination there was general loss of muscular tone and motor power; the arms were weak, the hand grip very impaired. The calf-muscles were flabby and flaccid, very tender on pressure; there was bilateral foot-drop but no wrist-drop. Sensory examination revealed analgesia to pin-prick, light^{touch} and thermal discrimination in the feet and legs to the distal third of the thigh, and analgesia proximally to just above the elbows in both arms. The ankle and knee-jerks were absent, the plantar reflex was flexor; the supinator and triceps jerks were absent and the biceps jerk was almost imperceptible. The pupils were equal, the reflexes normal and there was no apparent disturbance of the cranial nerves. Vibration sense was impaired in the lower limbs; there was no true ataxia, muscular weakness being more marked than inco-ordination. The pulse was 84 on admission; the heart was slightly enlarged, and there was a soft mitral systolic murmur; the ankles were slightly oedematous. Blood and cerebro-spinal Wassermann reaction were negative. The teeth were artificial, the tongue slightly furred posteriorly, red and bald; taste-sensation was poor, the appetite poor and meals were followed by gastric discomfort and flatulence. Blood-count revealed R.B.C. 4,400,000, Haemoglobin 76%, W.B.C. 7,800 and no cellular abnormalities in stained films.

Gastric analysis showed complete absence of free acid and a total acidity not exceeding 6, with abundant mucus.

Treatment.— Owing to anorexia a light diet, consisting mostly of milk, eggs, milk puddings and fruit was prescribed, and the constipation treated with enemata and laxatives. The lower limbs were protected by cradle and the foot drop corrected by light splinting. Vitamin B₁ (Hoffmann-la-Roche), 400 international

Units were injected subcutaneously daily. At the end of the third day there was a slight subjective improvement, and at the end of a week this was definite; tingling and cramps had decreased and the oedema had disappeared from the ankles; there was still marked difficulty in dorsiflexing the feet. At the end of the second week, the numbness had shrunk to the ankle-level, and pin-prick and light touch were appreciated below the knees; the fingers and hands felt warm and tingling sensations were confined to the finger tips. Ankle and knee-jerks were absent. In the meantime the appetite had considerably improved and a full, adequate diet with cereals, eggs, meat, milk and fruit was being taken. Parenteral vitamin B₁ was reduced to alternate days.

By the end of the third week the patient was able to walk a few steps with a suspicion of steppage gait, but the dorsiflexors were much stronger. There were no muscle cramps, though the calves were still hyperaesthetic to pressure. There was a general feeling of well-being. Two weeks later the patient was discharged; walking was accomplished slowly but steadily, and there was no longer any foot-drop. Both knee-jerks had returned but were weak, the ankle-jerks were absent. The fingers felt perfectly normal, all numbness having disappeared, and the tendon reflexes could all be faintly elicited. The soles of the feet were tender when pressed firmly on the ground, but during ordinary walking felt as if "padded".

The patient was instructed to take marmite daily and to return bi-weekly for vitamin B₁ injections. He was re-examined on September 24, 1936 and October 1, 1936. By the latter date he was able to walk a mile daily and to do light gardening; too much exercise resulted in a constricted sensation in the calf-muscles, and pressure on a spade was slightly tender to the soles of the feet. The hands and fingers were normal, and light touch was appreciated over the dorsa of the feet. In addition, the left ankle ^{jerk} could be elicited. The appetite was excellent and the patient confessed to feeling healthier than for some considerable time. There was an inward retraction of the apex-beat of $\frac{1}{2}$ " as compared with its position on admission; the mitral systolic murmur was present but no longer diffuse over the praecordium. The patient had three further

injections of vitamin B₁ at weekly intervals and then discontinued treatment. He was advised to report on return of any suspicious symptoms but has not reported since.

Comment.--

Alcohol was eliminated from the possible causal conditions of the polyneuritis owing to abstinence for twelve years; as an aetiological factor in contributing to the gastro-intestinal derangement and achlorhydria it is important, as in all probability were the attacks of malaria and enteric in 1915-16. There was no direct evidence of other toxic factors, nor was there evidence of any dietary deficiency; both at sea and inland he had received plentiful supplies of vitamin containing foods. The long history of chronic gastritis, the precipitation of the illness by an acute exacerbation and severe vomiting, and the associated achlorhydria appear to be important factors. The transient attacks at sea, the history and course of the above illness, and the rapid response to big doses of parenteral vitamin B₁ indicate a deficiency of this factor, and suggest that the condition was closely allied to true beri-beri, both in cardiac, anorexial and polyneuritic manifestations. The response to parenteral treatment suggests that malabsorption was conditioned by the gastro-intestinal derangement.

Alcohol and Diabetic Deficiencies.

Case 11. A male patient, aged 53, was admitted on August 30th, 1936, to Ward 32 in the Edinburgh Royal Infirmary.

Patient was a music hall artiste by profession and complained of general tiredness, numbness and tingling in the fingers, toes and feet, and tendency to drop articles.

History.- Five years ago he began to develop tingling sensations and "pins and needles" in the feet and legs, which gradually spread up to the groins. The skin was very tender to the touch and friction of clothes produced sensations comparable to "electric shocks". Long silk stockings were worn day and night to obtain relief. Similar sensations later appeared in the fingers and hands. The condition was diagnosed as neuritis and treated by drugs, without much relief. Two weeks later his own doctor at home discovered the associated diabetes. As he took a liberal, though not excessive amount of alcohol, he was advised to cut down the latter to a minimum, and was dieted for the diabetes. He learnt how to test his own urine and for long periods was sugar free. The neuritis improved without disappearing; he was able to discard his silk stockings in May 1935, though slight numbness and tingling persisted up to the knees, and have been constantly present in the fingers for three years.

Owing to change of venue each week, the strict adherence to his prescribed diet is difficult and at times impossible. For the past few months he has grossly neglected his dietetic necessities, and has taken whisky more frequently. His diet has consisted mainly of bacon, kippers, sardines, biscuits, milk, tea, coffee but no sugar. The appetite has been poor and he had developed the habit lately of subsisting for days on morsels of food and alcoholic drinks.

On examination, blood-sugar estimations showed a "curve" of 173, 260, 320 and 240 mgms.% at half-hourly intervals following glucose ingestion. He was given a 1500 calorie diet (R.I.E., B15) and the urine was sugar-free in 24 hours.

Blood and cerebro-spinal fluid examinations revealed negative Wassermann reaction.

The lower limbs showed little evidence of wasting, motor movements were normal; the muscles were hyperalgesic to deep pressure. There was marked sensory loss to pin-prick and light touch from the toes proximally to a level immediately below the knees. Knee- and ankle-jerks were absent, the plantar reflex flexor. There was a loss of vibration sense in the right leg, and an impairment in the left. In the upper extremities the finger-tips were analgesic and there was impaired sensibility to the base of the thumb level. The biceps and triceps jerks were sluggish, the supinator jerks absent. Abdominal and papillary reflexes were normal, and there was no cranial nerve derangement. The fundi were normal.

Blood examination showed a slight secondary anaemia, and no cellular abnormalities in stained films. Cardio-vascular and respiratory systems were normal.

The tongue was slightly furred and red, with some papillary atrophy. There was a history of chronic obstinate constipation. Gastric analysis showed entire absence of free acid and low acidity of 12, with large mucous deposits in each fraction.

A diet of 1500 calories, rich in all vitamins, was prescribed; the main ingredients were milk, vegetables, eggs, lean meat, bacon, oatcake and butter, inclusively equivalent to over 5000 mgm.-eq. (Cowgill), i.e. 250 international units of vitamin B₁ daily. This was reinforced by the parenteral administration of 400 I.U. (Hoffman-la-Roche) daily.

The response to this treatment was the most dramatic of all the cases treated. After three injections of vitamin B₁ all numbness and tingling had receded to the distal phalanges in the fingers. After seven injections, the only subjective symptoms were a blunting of sensation in the extreme tips of the fingers and toes. He was able to stroke the lower limbs without the customary prickly sensations; there was marked return of sensory appreciation to touch and pin-prick in both extremities. There was no alteration in the reflexes; vibration could be faintly distinguished now in the right lower limb. Tenderness on deep pressure of the calf muscles was not so marked as on admission.

The shrinkage of the area of the paraesthesia from the wrists to the finger-tips was described by the patient as "like a glove being drawn off the hand".

The diet was increased to 1900 calories and 2400 calories (R.I.E., C24) without reappearance of glycosuria.

As the patient was much improved, and anxious to re-join his theatrical company, he was discharged eight days after admission.

Comment.--

The factors most actively concerned in this patient's neuritis were referable to diabetes, alcohol, dietetic neglect and achlorhydric gastritis. In the early stages the neuritic symptoms partially responded to diabetic dieting, though it persisted even when sugar-free. The larger consumption of alcohol probably aggravated the gastro-intestinal disorder and precipitated some exacerbation of symptoms. The association of a vitamin B₁ is almost dramatically suggested by the rapid sensory response to its parenteral administration.

Case 12. Polyneuritis associated with Diabetes Mellitus.

A male patient, aged 63, was examined in the Diabetic Department of the Royal Infirmary on February 26, 1937, where he had been attending as an out-patient for several years. His diabetes was of several years standing, but was now controlled by a diet of 2327 calories (R.I.E., C23 diet) without insulin; there was occasional glycosuria. He was able to follow his occupation as a commercial traveller.

He had suffered from nervous symptoms for two to three years, which were gradually becoming more pronounced. There were numbness, tingling and pricking sensations in both feet, extending less markedly to the knees; "pins and needles" sensations in the finger-tips, and numbness; lately loss of sensation in the fingers was so pronounced that he was tending to drop small articles. In addition, neuralgic pains and cramps in the calf-muscles were daily complaints. All symptoms were brought on or exaggerated on retiring to bed, and almost every night sleep was disturbed. Relief was partially obtained by rubbing the hands and legs vigorously. For two months, there had been slight swelling of the feet and ankles at night, when the boots were found to be tight; the swelling had disappeared by morning.

On examination, the pulse was 70, the radial arteries decidedly thickened and sclerotic. There was analgesia to pin-prick and light touch from the knees distally, most marked over the dorsa of the feet and toes. The calf-muscles were very tender on deep pressure. The finger-tips were anaesthetic to light touch, and there was impaired sensitivity to pin-prick and touch to the wrist-joint level. The knee-jerks were diminished, the ankle-jerks absent, the plantar response flexor. The biceps-jerks were elicited with difficulty, the triceps and supinator jerks absent. There was a general loss of muscular tone, the calf-muscles being distinctly flabby. The gait was normal, slow but not ataxic, and there was no Rombergism.

The pupils reacted to light and accommodation and were equal in size and regular. The cranial nerves were normal. There was no cardiac enlargement, and no

murmurs; there was slight oedema in both ankles.

The tongue was clean, smooth and not tremulous. The appetite was good, but the patient was chronically constipated, and suffered from distension, discomfort in the stomach, and flatulence after meals; no fluid was taken with meals as this aggravated the dyspepsia; the teeth were artificial. Fortunately the patient was intelligent and willing to co-operate. He came into hospital for gastric analysis later and was found to have a total absence of free hydrochloric acid, and a total acidity of 6 (maximum).

Blood estimation of bisulphite binding substances showed an amount of 2.06.mgms.%.
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The patient's diet was calculated for vitamin B₁ content and found to contain 5565 (approx.) Cowgill mgm.-equivalents. The calorie value was 2327; these values did not include small amounts of Marmite taken daily. The VIT/CAL ratio was therefore 2.39, adequate in vitamin B₁ content, according to Cowgill's prediction chart, for a man weighing 86 kilograms, and more than adequate for the patient, whose weight was 10 stones 12 lbs. (70 kilograms). The addition of marmite to the calculation would have still further increased the VIT/CAL ratio; the minimal value was deemed preferable.

In treatment, no alteration was made in the diet: 1000 international units of vitamin B₁ ("Betaxin") were administered on the first visit, and the patient instructed to inject 500 units daily.

A week later, a further blood examination showed a slight reduction in bisulphite binding substances from 2.06 to 2.02. Subjectively the patient was not certain as to any improvement; if anything, the "pins and needles" sensations in the finger tips were less noticeable and the feet were, if anything, more comfortable.

The patient was seen again a week later (after two weeks' treatment). The cramps in the legs had improved perceptibly and he had^{had} three or four consecutive nights of unbroken sleep. The tinglings and cramps had appeared as usual after retiring to bed but not so severely or so persistently and he was delighted at

securing relief during the night. The sensory abnormalities in the fingers had diminished and there was no longer the "dead" feeling in the tips. He felt more active and lively in himself, and attributed this to better nights. On examination there was still impaired cutaneous sensibility to touch and pin-prick in the fingers, ^{but} there were no anaesthetic areas as on the first visit. The ankle-jerks were still absent, and the calves tender on pressure.

It was at this stage that the patient was found to be achlorhydric and one dram doses of ac. hydrochlor. dil. were prescribed twice daily with food. The vitamin B₁ was reduced to 500 I.U. on alternate days parenterally. At the end of the fourth week of treatment, further slight improvement was apparent. The knee-jerks were brisker but not normal, and the right ankle jerk was faintly elicited, as also were both triceps-jerks, the supinator remaining absent. Slight numbness was still present in the finger-tips but had disappeared from the rest of the hands. Cramps in the calves were still present but were much improved compared with their severity and frequency on his first visit; the toes still felt numb, but the tingling was much reduced. Swelling of the ankles at night still persisted, and slight oedema of the subcutaneous tissues around the ankle was found on examination.

The patient was advised to inject 500 units of vitamin B₁ twice weekly (more frequently if he could afford the cost) and to take marmite regularly every day. He has been seen twice since, at weekly intervals, and no further change was found. Subjectively, improvement in cramps, neuralgic pains, insomnia and tingling sensations has been maintained though not cured; objectively, there has been shrinkage of the areas of sensory loss to the periphery and a slight improvement in the deep tendon reflexes.

Case 13. Polyneuritis associated with Diabetes Mellitus.

A male patient, aged 48, was seen in the Dietetic Out-patient Department on March 5, 1937. He has suffered from diabetes for several years, which is controlled by a diabetic diet of 2300 calories, and one injection of 20 units of insulin daily. He has been treated as an out-patient throughout. In addition, for the past year he has complained of painful cramps in both legs, numbness, tingling and "pins and needles" sensations in the feet, gradually diminishing towards the knees. Occasionally there was slight tingling in the finger-tips. The cramps in the calf-muscles often prevented sleep.

On examination there was sensory impairment to pin-prick and light touch over the dorsum of the feet, extending to a level just distal to the knees; the calf-muscles were very hyperaesthetic to deep touch, and there was some atrophy. The knee-jerks were diminished and sluggish; both ankle-jerks were absent; the plantar response was flexor. Rombergism was absent; and there was impaired vibration sense in both lower extremities.

The pulse was 74, regular and well-sustained; the radial arteries were slightly thickened.

The appetite was good; there was no gross indigestion but a feeling of distension after food. The bowels were constipated. The tongue was clean, slightly dry and tending to smoothness, with some papillary atrophy. Gastric analysis could not be made, owing to the patient's inability to come to the Royal Infirmary as an in-patient. The gastric symptoms and appearance of the tongue were suggestive of hypo- or achlorhydria, and it was regrettable that the gastric acidity could not be investigated.

Blood was taken for bisulphite-binding-substances estimation and found to contain 3.03 mgm.%.

His diet (C23, R.I.E.) contained an abundance of vitamin B₁ (in the form of oatcake, porridge, bacon, eggs, lean meat and marmite) and all other vitamins. It was considered unnecessary to calculate the VIT/CAL ratio.

No alteration was made in the diet. The patient was given parenterally 100 I. units of vitamin B₁ ("Betaxin") and a supply sufficient to allow of 500 units daily, to be injected subcutaneously with insulin.

He was seen at the out-patient department one week later. The muscular cramps had diminished to such an extent that for the past three nights he had had unbroken sleep for the first time for months. The tingling in the feet had improved noticeably after the third injection. There was no alteration in the reflexes. There was no change in cutaneous sensibility in the feet but there was better appreciation of pin-prick in the proximal half of the legs. The calf-muscles were still very tender.

A second blood examination revealed a decrease in the amount of bisulphite binding substances from 3.03 mgm.% to 2.51 mgm.%.

Owing to the costly nature of the vitamin B₁ preparation, one ampoule was advised (500 I. units) on alternate days. The patient was seen again two weeks later and further improvement noted. Analgesia was confined to the feet and ankles; above this level pin-prick and light touch were now appreciated. The knee-jerks were more easily elicited though the ankle jerks were still absent. Tenderness in the calf muscles was still present, though not so severe as on the first visit. Cramps still occurred in the calves but were still more infrequent and were not so severe now as to interfere with sleep. There was no glycosuria on the visits referred to.

Further progress is being watched.

Comment.-

Polyneuritis developed and progressed in this case in spite of adequate vitamins in the diet. Parenteral injection of vitamin B₁ in large daily amounts caused rapid amelioration of certain symptoms, particularly cramps. It is difficult to say whether there was any degree of malabsorption without gastric analysis as a guide to stomach function, though this is suggested by the appearance of the tongue.

The striking fall in the blood B.B.S. following the cumulative amount of 4000 international units of vitamin B₁ is worthy of notice.

Case 14. Polyneuritis associated with Diabetes
and Alcoholism.

A male, aged 60, was admitted to Ward 22 in the Royal Infirmary, on October 21, 1936, in a semi-comatose condition. He had suffered from diabetes for about 5 years, and for two weeks prior to admission had been drinking whisky and methylated spirits heavily. He was drowsy but coherent when roused, but complained of severe frontal headaches.

Examination was purely objective at this stage. The urine was loaded with sugar, there was no albumen, and no acetone. Blood-sugar was 252 mgm. %. The pupils were regular, equal, and reacted to light and accommodation. The optic discs were normal. Other cranial nerves were normal. The pulse was 80; blood pressure 142/78. The tongue was moist and thickly coated, the teeth carious; spleen and liver were not enlarged; there was marked tenderness in the epigastrium. On fluids he became sugar-free on the second day. When rational he was found to be very depressed, the mental attitude poor. He had had tingling sensations and numbness in the feet and lower limbs for some weeks, and increasing weakness in the legs when walking. The patient was a poor co-operator and it was difficult to define the areas of sensory disturbance. There was definite anaesthesia to light touch over the feet and ankles, and there appeared to be diminished cutaneous sensibility to the level of the knees. The calf-muscles were tender, and some flaccidity of the muscles was present. The ankle-jerks were absent, the knee jerks sluggish, the plantar-reflex flexor. There was a faint supinator jerk, but the biceps and triceps jerks were absent.

A fractional test-meal showed the presence of free hydrochloric acid, varying from 20 to 60, and a total acidity from 50 to 80 - in 2 hours. The Blood Wassermann reaction was negative.

Further questioning revealed that the patient had had "self-harmful" tendencies during the 2 weeks prior to admission, had partaken of very little food, and had taken large amounts of sugar and treacle in addition to alcohol.

He was treated diabetically, the condition being controlled by a diet of 2300 calories and 52 units of insulin daily. No alteration in the reflexes was noted, and the muscle tenderness persisted, but symptoms referable to the lower extremities were overshadowed by the mental depression. The patient was discharged after 4 weeks feeling much better and mentally healthier.

He was re-admitted about a month later - on January 3, 1937 - in a state of coma. He had apparently relapsed into another bout of depression and had taken large amounts of port, whisky and methylated spirits. We were informed by a relative that he had not kept to his prescribed diet but had nevertheless had his insulin regularly.

The urine contained albumen, sugar, acetone and hyaline casts. Following the usual treatment for diabetic coma, the patient became rational. To the complaints of his first attack were now added dyspnoea, palpitation, retrosternal pain, swelling of the ankles, almost complete anorexia; increase of tingling sensation in the lower limbs, shooting neuralgic pains and cramps in the calf muscles, causing insomnia. Tenderness in the calves was very marked; the muscles weak and flabby, but co-ordination not affected. Knee, ankle, biceps and triceps jerks were absent; there was a slight supinator response. The same cutaneous sensory impairment in the lower limbs was found, and in the arms to a point distal to the elbow, but again lack of co-operation made accuracy in defining the extent of sensory loss difficult. There was no foot or wrist drop, but marked weakness of the dorsiflexors.

The diabetes was controlled by a diet of 1900 calories and 52 units of insulin daily.

Fifty units of vitamin B₁ (Vibex) were injected daily. Ten days later (January 15, 1937) the amount of insulin had been reduced from 52 to 30 units daily without glycosuria. On January 23, 1937, the diet was increased to 2500 calories, and this was controlled throughout until his discharge by 40 units of insulin daily.

There was little improvement in the polyneuritis for the first three weeks, except that daily examination

of the reflexes revealed a return of the biceps jerks on January 21, 1937, - the 15th day of parenteral vitamin treatment. On the 24th day, all the upper limb deep reflexes had returned, though sluggish. The calf-muscles were still tender but cramp pains were less severe and very infrequent, and the tingling sensations in the feet had decreased. On the 14th of February (the 40th day of treatment), though still weak, the patient was able to walk well and was generally stronger. The muscle cramps were very infrequent, there were no shooting pains in the limbs; the calves were still tender but much less than on admission, and the soles of the feet felt somewhat numb. It was still difficult to secure co-operation in defining sensory impairment, but pin-prick was more easily distinguished below the knees. The biceps, triceps and supinator reflexes had fully returned; the deep reflexes in the lower extremities were unusual in that both ankle-jerks could now be faintly elicited and also the right knee-jerk; the left knee jerk was still absent.

The patient was discharged on February 15, 1937, after 41 days' treatment.

Comment. It was impossible to ascribe the polyneuritis to any particular factor in this case; there were toxic (teeth), uncontrolled diabetic, alcoholic and psychological factors present; it was impossible to make any previous dietary calculation - the appetite had been capricious and then frankly bad, he had lived for days on mere mouthfuls of food and before admission had wilfully engorged sugar and treacle. Though one can assume a general dietetic deficiency, no attempt was made to calculate calorie or vitamin values.

Though the polyneuritic condition was more severe on his second visit as judged by his own evidence and the absence of reflexes, treatment was more satisfactory following the same dietary - insulin regime, with additional parenteral vitamin B₁, than by dietary-insulin measures alone on his first visit, and the return of tendon reflexes was striking. Applying Cowgill's formula to the prescribed diabetic diet, made up of milk, vegetables, eggs, lean meat, bacon, butter, oatcake, there was a calorie value of 1936 and a vitamin B₁ content of (approx.) 5,266 mgm. equivalents (Cowgill). This gives a VIT/CAL ratio

of 2.7, adequate for a man weighing 96 kilograms. The weight of this patient was 10 st. 10 lbs. (70 kilograms) so that by diet alone he was having more than the predicted requirement, which (2.7) actually is adequate for a weight of 96 kilograms. The addition of 50 i.u. of vitamin B₁ added 1000 mgm. equivalents, and thus increased the VIT/CAL ratio to 3.3, adequate for a weight of over 110 kilograms.

The slow response to treatment (3 weeks) may have been due to several factors; though the glycosuria was controlled, this alone may not have influenced the polyneuritis, as is evidenced in numerous cases of diabetic neuritis. The hospital diet contained adequate vitamin B₁; this may have been only partially absorbed owing to gastro-intestinal defects consequent upon alcoholism, of which there was a long history with two recent bouts of exorbitant drinking; on the other hand, the stomach was secreting well, as judged by free and total acidity. Again, 50 international units of vitamin B₁ parenterally daily may not have been sufficient to effect a quick response; after improvement began, however, it was satisfactory and maintained. The main factors concerned were probably the withdrawal of alcohol, the control of the diabetes by diet and insulin, and intake of an adequate diet with parenteral vitamin B₁. These factors were all concerned during his first visit to hospital, with the exception of parenteral vitamin B₁; the fact that more pronounced improvement was made in the nervous condition when the latter was added to his second course of treatment indicates that this factor was concerned in that improvement.

Case 15. Polyneuritis associated with Anaemia
and Achlorhydria.

A female patient, aged 45, was admitted to Ward 24 in the Royal Infirmary.

The outstanding symptoms were general tiredness, breathlessness and palpitation on slight exertion for over a year, and for the last month swelling of the feet and ankles. Exertion was attended by a gnawing pain over the heart, radiating upwards into the left side of the neck and across towards the right armpit; this was worse after a hard day's work and relieved by rest. A difficult labour 14 years previously had been followed ever since by a vaginal discharge and painful menstrual periods. For three years she had suffered from attacks of pain on passing water, pains at the bottom of the back, and the passage at these times of a milky offensive urine. There was a six months' history of pruritus vulvae. For several months there had been severe headaches and 'tiredness' of the eyes. Three months prior to admission she began to experience numbness, tingling, and 'pins and needles' sensations in the hands and feet. Sometimes there were painful pricking pains in the tips of the fingers which made work difficult and uncomfortable. For a few weeks the fingers had been cold and numb, and the feet felt as if they 'had gone to sleep'. There was a numb, 'padded' sensation in the soles of the feet whilst walking. The tingling extended proximally to the calf muscles, and at night she had occasional attacks of cramp in the legs.

Her appetite had been good until a few months before admission. She did not suffer from pains after food, but always felt distended after the heavier meals and often brought up large quantities of "wind". She had always had a tendency to constipation, though never severe. Lately she had incurred a distaste for food, and often felt sick without actually vomiting.

Family history: She was one of a family of seventeen children, ten of whom died in infancy; one died later of gall-stones and one was killed. She herself had five children, all alive and well.

On examination, patient was obese, weighed 12 stones 13 lbs. and was obviously anaemic, the skin possessing a lemon-yellow tinge. All the mucous membranes were pale.

Blood: R.B.C. 3,500,000. haemoglobin 36%. Colour index .5. W.B.C. 6,000, normal differentiation. The stained film was interesting in that though the red cells were mostly microcytic and poorly filled, there were many large megalocytes, and some degree of polychromasia. No nucleated red cells were seen. Reticulocytes numbered 16 per 1000.

Alimentary System: The tongue was clean, smooth, pale and atrophic. Fractional test meal showed achylia gastrica after histamine (.5 mgs.) injection. The teeth were carious and pyorrhoea was present in the gums. The abdomen was flabby, of poor musculature; there was no enlargement of liver or spleen. The systolic blood pressure was 106, and the diastolic 60; the apex beat was in the 6th intercostal space, beyond the mid-clavicular line, and there was a soft systolic mitral murmur.

The blood Wassermann reaction was negative, and there was an icteric index of 10. The urine contained albumen, epithelial cells and gram positive cocci, and a growth of *Staphylococcus Albus* was obtained on culture.

The main points elicited by examination of the nervous system were the flabbiness of the calf-muscles and the abnormal tenderness on deep pressure. There was peripheral sensory impairment to light touch and pin-prick in the fingers and over the dorsum of the feet, present but less marked at the wrists, and to a level about 9" proximal to the ankles, of typical "glove and stocking" distribution. Vibration sense was deficient in the lower limbs. The biceps, triceps and supinator jerks were present and normal. Both knee jerks were difficult to elicit, as was the right ankle jerk; the left ankle jerk was absent. The plantar reflex was flexor.

Treatment: The patient was given a nutritious diet of fish, chicken, rabbit, collops, meat, fruit, vegetables and milk puddings; Acid hydrochloric dil. 3i. t.i.d. in orange juice with meals. Iron was given in the form of Tab. Ferri Sulph (Glaxo) gr.ii. t.i.d.

The blood response to this treatment was as follows:-

Feb. 21	R.B.C.	3,700,000	Hb. 46%	Reticulocytes	3.7%
" 27	"	4,300,000	" 58%	"	4.6%
Mar. 6	"	4,900,000	" 67%		
" 12	"	5,000,000	" 70%	Colour Index	.7

From a neurological point of view it is interesting to note that on March 4th when the red cell count was (approx.) $4\frac{1}{2}$ millions and the haemoglobin about 65%, the symptoms of peripheral neuritis had shown little improvement; numbness, tingling and 'sleepiness' of the hands and feet were still present, though the cramp-like pains in the calves had gone. Examination still showed sensory loss or impairment as on the first examination, and tenderness on pressure of the calf muscles persisted.

The patient was now given 2 c.c. "Benerva" (Bayer) containing 1000 units of vitamin B₁ for three consecutive days, on the 4th, 5th and 6th of March. There was an immediate improvement. After three injections the tingling and 'pins and needles' sensations had gone completely from the hands, and only a feeling of numbness remained in the tips of the fingers. Similarly in the lower limbs the paraesthesia disappeared from the legs, ankles and dorsum of the feet, leaving slight numbness in the toes and in the soles of the feet. The dose of vitamin B₁ was reduced to 1 c.c. (500 units) daily and stopped altogether on the 10th of March. The knee jerks were brisker, and the left ankle jerk could now be faintly elicited. The patient was able to distinguish pin-pricks and light touch over the feet and hands, and the only remaining symptom was slight numbness in the soles of the feet. There was still some deep tenderness on pressure of the calf muscles, though this was definitely diminished. (Treatment would have been continued, but the patient was transferred to the Gynaecological block for appropriate measures to relieve the menorrhagia, etc.)

Comment: The hypochromic anaemia was ascribed to the long history of menorrhagia, toxic factors from the sources mentioned, and inadequate absorption of iron which appears to be constantly associated with the achlorhydria and atrophic condition of the upper part of the alimentary canal in these cases. The pertinent doubt was raised as to the possibility

of this case advancing into the pathological condition of pernicious anaemia, for although the condition responded to iron therapy, the degree of megalocytosis in the stained film was far in excess of that seen in typical microcytic hypochromic anaemia; two clinicians, without any knowledge of the case but from examination of the blood film alone, considered the character of the cells not to be incompatible with pernicious anaemia, though not typical. Nor are there any other dissimilar features: the lemon tint of the skin, the general symptomatology, the flabby, well-nourished appearance, the icteric index, the achylia gastrica and the presence of peripheral neurological symptoms and signs are all features which figure largely in the clinical picture of pernicious anaemia. The neural findings were obviously of greater degree than could be ascribed vaguely to 'poor circulation', 'peripheral anaemia', 'anoxaemia' and were in the nature of a true, early polyneuritis evidenced subjectively and objectively. Nor did they show much response to an improved blood condition, *per se*. On the other hand the parenteral administration of vitamin B₁ produced immediate benefit, as if anxious to bring about a return to normal function of nerve fibres which a combination of nutritious diet and haematinics had begun but had been unable to complete. A vitamin B₁ deficiency, probably conditioned by an atrophic state of the upper alimentary tract and malabsorption, seems a reasonable surmise to make.

Lastly, from a study of the etiological and clinical factors in this case, it is pertinent to ask, though impossible to prove, whether, if this patient had been left untreated for several months, she would not have presented eventually a clinical picture of pernicious anaemia and a neurological complication identifiable as early subacute combined degeneration of the spinal cord. For the moment we must be content with a diagnosis of idiopathic hypochronic anaemia and peripheral neuritis, though the distinction is surely a very narrow one.

The value of early vitamin therapy in this type of case as an adjunct to haematinics is obvious, both prophylactically and curatively.

Case 16. Subacute Combined Degeneration of
the Spinal Cord.

A female patient, aged 56, was admitted to Ward 33 on August 27th, 1936, with manifestations of subacute combined degeneration.

Her occupation was that of a school cleaner until a year ago.

History: She was admitted to Edinburgh Royal Infirmary in May 1935 with pernicious anaemia and successfully treated with liver therapy for six weeks. She was discharged after an excellent response to treatment and advised fully about continuing her treatment with liver extract.

Three months after discharge (i.e. 9 months ago) she began to experience tingling, numbness and 'pins and needles' sensations in her feet and ankles which gradually spread upwards to the knees. This was accompanied by slight swelling of the ankles. She was staying at this time in the Orkney Islands and owing to difficulty in procuring supplies of liver extract had only been taking about half her usual quantity. Gradually the numbness of the skin and slight tingling extended higher, eventually involving the groins and now reaching up to the level of the umbilicus. Three months ago, walking, which had been getting more and more difficult, became "shuffling" in character, and attended with such a degree of unsteadiness that she had to stay in bed where she has since remained. In addition she suffers from occasional pains in the calf muscles, particularly on attempting to move the legs quickly. Two months before admission her fingers, which had hitherto been free from symptoms, were similarly attacked. At first, there were attacks of tingling, 'pins and needles', and alternating sensations of burning and cold. The finger tips now felt numb, but were tender when subjected to pressure, and the hand was tender when squeezed. The numbness had extended to the elbows in both arms.

Otherwise few symptoms were complained of, although the appetite had been poor for some time. Six weeks before admission her doctor gave her a course of six intramuscular injections of liver, but she was not conscious of any improvement.

On Examination: The blood revealed R.B.C. 4,530,000. Hb. 80%. Colour index .9. Reticulocytes 1%. Stained film showed tendency to megalocytosis; no nucleated R.B.C. were seen; and some slight degree of anisocytosis was the noticeable feature.

The tongue was typical of pernicious anaemia, clear, flabby, smooth and bald.

Fractional Test-Meal showed an entire absence of free hydrochloric acid in all fractions.

Examination of the nervous system revealed a slightly spastic condition of the legs, with marked muscular wasting, and tenderness on deep pressure of the calf muscles. There was marked loss of position sense in both limbs, and of vibration sense. The limbs could be moved by the patient only with difficulty and pain. There was analgesia to pin-prick and light touch from the toes to the knees, most marked at the periphery, and less impaired sensory discrimination over the skin of the thighs extending over the trunk to the level of the costal margin. The knee and ankle jerks appeared normal but it was surmised from the obvious involvement of both posterior and lateral columns of the spinal cord, that the tendency to loss or diminution of the reflexes consequent upon the sensory degeneration was offset by the tendency to exaggeration of the reflexes by involvement of the pyramidal tracts, thus producing what appeared at first sight to be normal reflexes. The plantar response was extensor on both sides.

In the upper extremities, there was peripheral sensory loss extending to the axillae, most marked from the fingers to the wrists which were almost anaesthetic to light touch. There was definite lack of co-ordination when fine movements with the fingers were attempted, and the patient admitted to being 'clumsy' at using her hands. The biceps, triceps and supinator reflexes appeared normal as in the lower limbs.

Liver treatment was withheld and the patient given 500 units of vitamin B₁ daily parenterally. The blood was examined daily but at the end of a week (after 3500 units) there was no change in the blood picture and no increase in the number of reticulocytes.

The principal response to vitamin B₁ treatment was the shrinkage of the subjective sensations of numbness on the abdomen down to the groins, and in the upper extremities, from the axillae to the elbows. These were the last areas to develop parasthesia and the first to show any beneficial effect. In addition there was a slight improvement in the periphery, the tingling in the fingers and toes being less marked. At the end of the second week of parenteral vitamin treatment, there was more freedom of movement in the fingers and an admission of there being 'more life in them'; there was improved sensibility to pin-prick and light touch distal to the elbows, though this was still markedly impaired distal to the wrist. Similarly in the lower limbs, dorsiflexion of the ankle was easier and attended by less pain, and appreciation of pin-prick and light touch improved below the knees; proximal to this level sensation was now almost normal. There was no change in the character of the deep tendon reflexes and the spasticity in the limbs was unchanged. During the third week of vitamin B₁ treatment the condition seemed to be stationary and no further improvement was noted. As the red cell count was by now showing signs of falling, liver treatment (Campolon) was given in addition to the vitamin B₁. A week later the patient, who was becoming mentally depressed, was discharged, and continuance of her treatment at home advised. She was unable to walk unsupported.

The prognosis in this case was not good; there was obviously marked involvement of both posterior and lateral columns as shown by the spasticity, potentially increased reflexes, Babinski sign, loss of vibration sense, impaired muscle position sense and the extensive sensory involvement. Nevertheless there was a very noticeable response to parenteral vitamin B₁ treatment, though this was confined almost entirely to the sensory elements and to subjective rather than objective phenomena. The more recent disturbances of cutaneous sensibility in the abdomen and thighs and in the upper arms almost disappeared, whilst after four weeks there was some improvement in the severity of the symptoms in the periphery. It must be noted too that no liver therapy was prescribed during the first three weeks.

As regards dietetic factors, this patient had always been well cared for and had had a sufficiency

of good food; in fact though not a big eater, she was fond of foods containing vitamin B₁, eggs, cereals, meat, milk, etc.

On the other hand there was presumably a long history of gastric abnormality as evidenced by achylia gastrica, and even the slight response to parenteral vitamin B₁ suggests that this factor in the diet, though important, was imperfectly absorbed. Hospital treatment could not be prolonged, as the patient was becoming depressed. A continuance of the parenteral method of treatment was advised, but probably the exigencies of domestic economy have prevented its further use. The extent to which more improvement could be expected in a patient showing marked degenerative changes is doubtful, and it is regretted that circumstances prevented a continuance of treatment under observation in hospital.

Case 17. Peripheral Nerve Degeneration associated
with Diabetes, Pernicious Anaemia and
Subacute Combined Degeneration of the
Spinal Cord.

A female patient, aged 68, was examined in the Diabetic Out-patient Department of the Royal Infirmary on February 26, 1937. She had suffered from diabetes for about 15 years. About 1932 she noticed she was getting weaker rapidly. Medical examination revealed an anaemia of the pernicious type, for which liver extract therapy was instituted and the anaemia improved. During all this time she had had vague tinglings, and numbness in the extremities.

In spite of control of the diabetes and liver therapy, the nervous condition gradually progressed and affected her walking. She was admitted to the Royal Infirmary and found to have subacute combined degeneration of the cord, and achylia gastrica.

Her glycosuria was now controlled by a diet of 1968 calories, with a ratio of carbohydrate, 94; protein 74; and fat 144.

On examination, there was marked spasticity, especially in the lower limbs, and walking was only accomplished with the greatest difficulty. The muscles were markedly atrophied, and all the deep tendon reflexes exaggerated; the plantar reflex was extensor bilaterally. There was a gross loss of position and vibration sense. Numbness was complained of from the feet to the knees and the legs and hands always felt cold. Sensory loss to touch and pin-prick was found in both lower limbs to a level of a few inches proximal to the knees.

Her diet contained a vitamin B₁ content of over 5000 Cowgil mgm.-equivalents, and 1968 calories, giving a VIT/CAL ratio of 2.5 and adequate for a body-weight of 88 kilograms. As this patient weighed only 62 kilograms, her vitamin B₁ dietary supply was more than adequate.

The patient was receiving the maximum possible amount of treatment in the form of liver injections and oral extract, and the glycosuria was controlled. She

had to be assisted in her visits to the Infirmary, being unable to walk without support, and consequently was only able to come once a month. Her finances were severely taxed, and in consequence of the extensive degenerative spinal cord and nervous degeneration, it was not deemed prudent to tax her resources still further by embarking upon a necessarily protracted course of parenteral vitamin B₁ treatment.

I have drawn attention to this case on account of the nature of the complex - diabetes, pernicious anaemia and subacute combined degeneration, associated with achylia gastrica. And secondly, extensive nervous degeneration had taken place and was slowly progressing in spite of adequate dietary measures, rich in all vitamins, and containing an abundance of vitamin B₁, according to Cowgill's predicted requirement.

Case 18. Subacute Combined Degeneration of the
Spinal Cord.

A male patient, aged 39, was admitted to Ward 22 in the Royal Infirmary of Edinburgh on February 26th, 1937.

He was complaining of constant frontal headaches, dimness of vision, marked general weakness, particularly in the legs, and numbness and tingling in the feet. He had no taste for food, was losing his powers of concentration and becoming depressed. These symptoms had been intermittent since 1935, except the eye defect which had been constant. His previous illnesses included influenza and pneumonia in 1918, since when he has had a slight constant cough. He takes alcohol very sparingly but has always been a heavy cigarette smoker.

In 1935 his main symptoms were headaches and dimness of vision, and, in the lower limbs, tinglings and numbness of the feet and ankles. He was actively employed in a rubber (motor-tyre) warehouse. His own doctor thought the condition might be a polyneuritis and eye-defect of a toxic nature associated with carbon-bisulphite or benzene poisoning, but these possibilities were eliminated by investigation. He was found to have complete loss of sense of taste and smell; eye examination revealed paracentral scotomata and bilateral papilloedema. Special investigation revealed the unlikelihood of cerebral tumour. Tobacco ambliopia and Leber's disease were further suggestions. In 1936, blood examination revealed only a slight degree of anaemia but films showed a tendency to megalocytosis and poikilocytosis. He received an intensive course of liver therapy (Pernaemon forte) but the diagnosis of early pernicious anaemia appeared doubtful; there was no response in the red cell count, and the colour index remained over unity (1.1). The long rest in bed away from his work benefitted him considerably, however, and for many months he felt much stronger. Two months prior to his present admission, weakness became more marked, the appetite deteriorated; weakness in the limbs was now pronounced and he was admitted to hospital.

Until a month ago, in spite of inability to taste his food, the patient had taken nutritious food - "in deference to his wife's wishes". Eating was purely a habit but he was accustomed to good meals. The usual daily dietary consisted of bacon and eggs, toast, marmalade and milk-coffee for breakfast; porridge in winter; cocoa or coffee with milk at 11 a.m.; mince, beef or other meat, potatoes, vegetables and a milk pudding for lunch; and a "high tea" about 6 p.m. of salads, fish or meat, with stewed fruit, custard or a pudding. There was no question of the adequacy of this diet and vitamin B₁ and calorie contents were not calculated. His weight had been steady for several years.

Blood examination revealed R.B.C. 2,800,000, haemoglobin 74%; colour index 1.3; W.B.C. 5,600. Stained films showed megalocytosis, anisocytosis and poikilocytosis.

Gastric analysis showed complete achylia gastrica. The tongue was pale, smooth, showed papillary atrophy and the sense of taste was completely absent. There was marked impairment of vision; the optic discs were very pale, but there was no papilloedema. The sense of smell had also gone.

In the limbs there was loss of muscle tone and power, and slight wasting. There was sensory loss to light touch and pin-prick over the dorsum of the feet and the lateral surfaces of the legs from ankle to knee; sensory impairment elsewhere was not marked. Vibration sense was lost in both lower limbs. The knee and ankle jerks gave normal responses (cf. 1935, when ankle-jerks were absent and knee jerks sluggish); the plantar reflex was difficult to elicit owing to marked hyperaesthesia of the soles of the feet; performed with the lightest touch there was a slight extensor deflection of the great toe. There was a slight suggestion of spasticity in the lower limbs only. The biceps, triceps and supinator jerks gave normal responses.

The patient was intelligent and co-operative. In spite of the anorexia, he made valiant attempts to eat a light but nutritious diet and was given ac. hydrochlor. dil. 3ii t.i.d. in orange juice, with meals.

Vitamin B₁ ("Betaxin") 1000 international units were injected daily for three days, and afterwards 500 units daily. At the end of a week (during which 5000 units of vitamin B₁ had been administered) there was no subjective improvement. The feet still felt numb though there was little tingling, there was no urge to eat, and no improvement in the tiredness and general weariness. Examination of the legs, however, revealed the return of sensory loss, and pin-prick and light touch were appreciated in the legs distally to the level of the ankle; there was still sensory loss over the dorsum of the feet. The patient, who had previously suffered mildly from constipation, had two attacks of diarrhoea during the week but whether this was related to the vitamin B₁ is not known.

Intensive intramuscular liver therapy (Campolon) was commenced during the second week, and Tab. Ferr. Sulph. (Glaxo) ii t.i.d. The result was a gradual improvement in general well-being but a slow haemopoietic response. Sensation returned over the dorsum of the feet but persisted in the toes; there was no change in the reflexes after four weeks' treatment. At the end of March (five weeks) the red cell count had increased to 3,500,000 and the haemoglobin to 84%. The patient was able to walk easier and without undue tiredness, and felt much better. The headaches were greatly relieved (dark glasses were worn) but there was no improvement in the sight. Two weeks later he was discharged. The red blood corpuscles still numbered under 4,000,000. Analgesia of the toes persisted but the sensations of tingling were much less frequent. Walking was more rapidly performed and without undue tiredness, and relief from the headaches was appreciated.

Liver therapy (parenteral) and Vitamin B₁ (500 units weekly) are being continued by his own doctor. A personal communication from the latter is reassuring; strength is being maintained, the patient has bought a tobacconist's business and feels better than for the past two years.

Note: a blood estimation of bisulphite binding substances made on admission revealed B.B.S. 2.60 mgms.%. After 5000 units of vitamin B₁ there was a

decrease to 2.01.

Comment.- The nature of the commencement of the above illness is of chief interest; the first diagnosis made was that of polyneuritis probably of toxic origin, and these symptoms with the headaches and optic neuritis were paramount for a long period; there is no reference indicating whether the spinal cord was affected at this early stage. The association of an anaemia which eventually became pernicious, the gradual involvement of the spinal cord, and optic neuritis associated with achylia gastrica, is noteworthy. There was very little evidence of the beneficial effects of vitamin B₁ in this case; a slight decrease in the tingling sensations in the lower limbs, and rapid return of sensory appreciation in the legs before liver therapy was instituted, indicated the apparently reversible nature of the ~~early~~ degenerative process in certain nerve fibres. The involvement of the lateral columns was not a good sign, nor was the sluggish response of the blood to liver therapy. The case appears to be one of a very slowly progressive degenerative nature, and it is hoped that the arrest of the process which apparently took place will be made permanent by a continuance of treatment.

The reduction in the amount of bisulphite binding substances in the blood following vitamin B₁ treatment is also noteworthy.

Case 19. Nervous Complications of Pernicious Anaemia.

A male patient, aged 52, was admitted to the Chalmers Hospital, Edinburgh, on April 24, 1936. His immediate complaints were general muscular weakness, difficulty in walking through loss of power in the legs, tingling and numbness in the hands, feet and legs, a feeling of walking on rubber, clumsiness in finger movements, and a tendency to fall. Walking was only possible with sticks. These symptoms had been gradually getting worse for two years.

He had an interesting and confusing previous history. He contracted a syphilitic infection in 1908, and developed tabetic signs in 1932 - paraesthesia, anaesthesia and hyperaesthesia of the lower limbs with a strongly positive blood Wassermann reaction. He responded well to specific treatment with tryparsamide and bismuth. In December 1933 his reflexes were normal, the optic discs normal, the blood Wassermann weakly positive. The cerebrospinal fluid revealed a negative Wassermann, no increase in globulin, 1 cell per cmm. and Goldsol test 0000000000. He still had slight tinglings in the hands and further treatment was recommended. However, he defaulted in 1934, and did not return until early in 1935; he had the same sensory symptoms as before in the hands and knees, stiffness of the legs below the knees, sluggish knee-jerks and absent ankle-jerks. The blood Wassermann was weakly positive and accordingly specific treatment was re-commenced. There was no response to treatment, and the patient was admitted to Chalmers Hospital in the condition described earlier.

On examination, the cranial nerves were normal, the pupils were equal and reacted to light and accommodation; speech and articulation were normal. There was no nystagmus or ptosis, and no tongue tremor. There was marked loss of power in all limbs and the muscles flaccid. In the lower limbs, incoordination was marked, position and vibration sense were lost. The gait was ataxic and Rombergism was marked. There was neither spasticity nor gross hypotonia; the calf muscles were tender on pressure.

Cutaneous sensibility to pin-prick was impaired distal to the knees and there was anaesthesia on the

dorsum of the feet. There was also sensory loss from the fingers ~~and~~ to immediately proximal to the wrists.

Of the deep tendon reflexes, the biceps jerks were sluggish, the triceps and supinators absent. There was a normal abdominal reflex. The knee and ankle jerks were absent, and the plantar response was flexor.

The pulse was 82, the blood pressure 136/80. The tongue was large, pale and flabby and showed papillary atrophy.

Gastric analysis revealed a complete absence of free acid.

Blood examination: R.B.C. 2,700,000. W.B.C. 7,300. Haemoglobin 58%.

A diagnosis was made of pernicious anaemia and degenerative changes, apparently confined at this stage to the peripheral nerves and posterior columns; the flexor plantar responses and lack of spasticity were taken as favourable signs.

All therapeutic measures were commenced, consisting of Campolon injections twice weekly, Ferri et Ammon. Cit. gr.30 t.i.d., Ac. Hydrochlor. dil. and pepsin with meals; a full diet with lightly cooked liver, milk, eggs, cereals and fruits. Vitamin B₁ in doses of 400 international units were injected intramuscularly thrice weekly.

One month later the R.B.C. numbered $3\frac{1}{2}$ millions, the haemoglobin had increased to 73%. On June 23, 1936, two months after admission, the red count was $4\frac{1}{2}$ millions and the haemoglobin 95%.

There was a remarkable improvement in the limb weakness at the end of a fortnight; numbness and tingling were less noticeable in both limbs. At the end of a month he was able to walk a little without sticks; Rombergism was still present and there was still impaired position sense.

The patient left hospital and his own medical advisor arranged to continue with his treatment; fortnightly injections of Pernaemon forte and 400 units of Hoffman-la-Roche vitamin B₁ were to be

administered twice weekly. A month later the knee jerks and the right ankle jerk had returned, as also had the triceps and supinator; the plantar reflex was flexor; walking was slow and slightly unsteady but could be accomplished more confidently and without support.

Blood examination showed R.B.C. 5,100,000 and haemoglobin 100%. The vitamin B₁ injections were now given at weekly, and Pernaemon forte at monthly intervals. The appetite and well-being were maintained.

This patient was seen last in January of the present year. He still experienced occasional tinglings in the fingers and feet but never ~~to~~ with discomfort; there was slight stiffness in the knees, but this was improving. Position sense showed improvement and vibration could be very faintly appreciated. Sensory impairment was confined to the toes, and pin-prick was easily discerned on the dorsum of the feet.

The left ankle jerk was still absent; the other deep tendon reflexes could be easily elicited, but there was no tendency to briskness or exaggeration. The plantar response remained flexor.

The blood condition was maintained at 100%, and the patient had improved to the extent of walking two miles a day.

A continuance of treatment was strongly advised.

Comment. This case illustrates the similarity of features of polyneuritis, the flaccid early nervous signs associated with pernicious anaemia, and the sensory phenomena of certain cases of locomotor ataxia. Whether the patient had congenital achlorhydria, or whether this condition was a slowly developing one is not known. We can assume a complete achylia gastrica about 1933, and the precipitation of pernicious anaemia, and with these pathological changes a state of conditioned deficiency and imperfect assimilation and absorption of essential nutrients, irrespective of the diet and the appetite, which was admittedly poor. One hesitates to use the term subacute combined degeneration as applicable to this case. Evidence of degenerative changes in both peripheral nerves and the posterior columns, there

was, in the Rombergism, lost vibration and position senses, ataxia, and absent reflexes. But there was a marked absence of signs pointing to involvement of the pyramidal tracts; one of the most pleasing features was the persistent plantar flexor response in spite of other reflexes returning. The quick improvement of numbness, tingling, and shrinkage of the areas of sensory loss to the periphery, as has been noted in polyneuritis, following vitamin B₁ injections, indicates the significance of this factor in the aetiology. It is doubtful whether liver and iron therapy alone would have procured such a rapid response in the nervous manifestations, and I think it can with safety be said that the nervous degenerative lesions in this case were not only arrested but considerably diminished. With persistent achylia gastrica, however, treatment by the parenteral method is essential if progress is to be maintained.

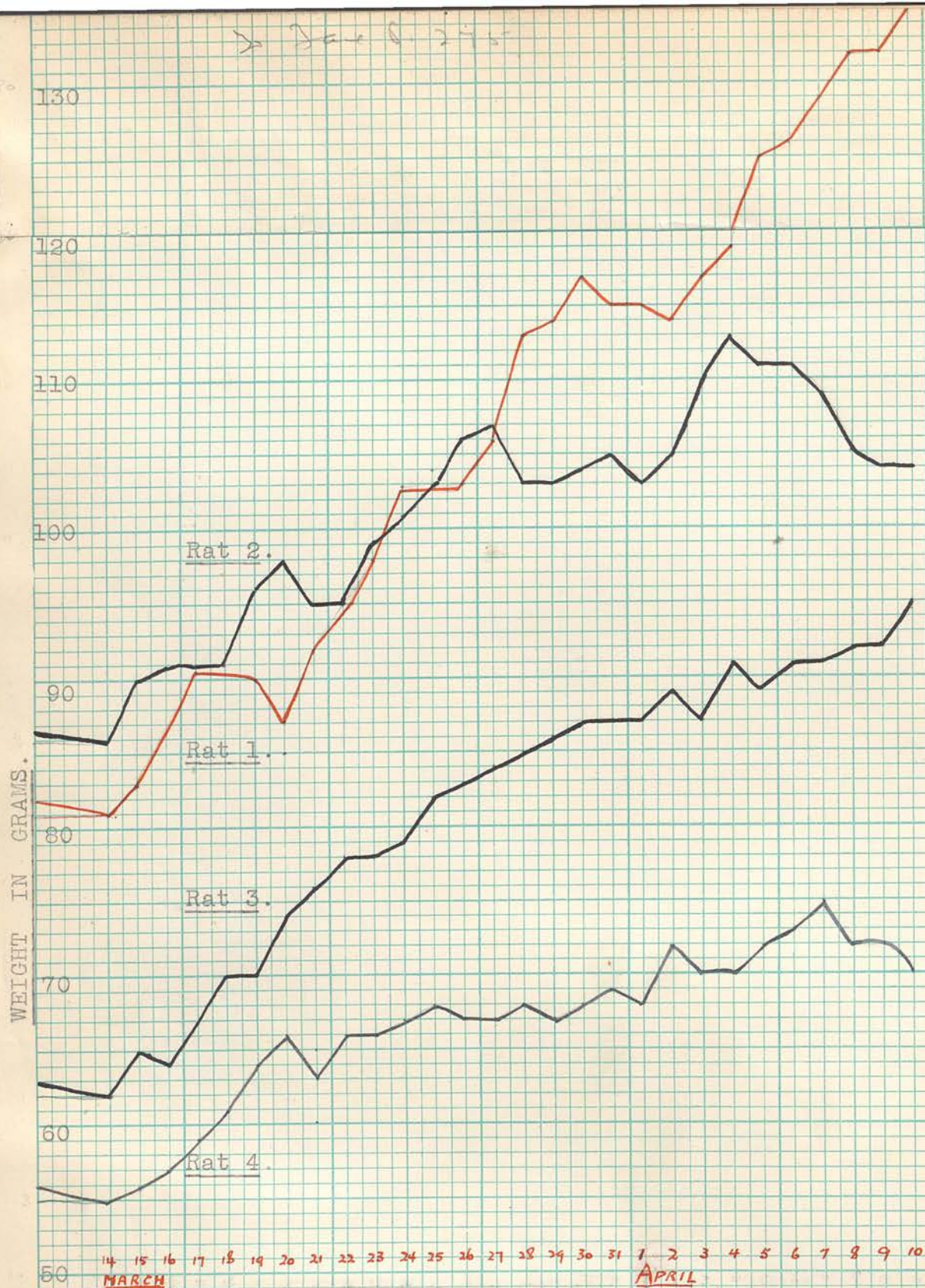


CHART 2

Chart illustrating the growth of four rats on solutions of vitamin B₁ in the normal and achlorhydric and acid fasting juice.

Rat 1. — Fed Solution I.
 Rats 2 and 3. — Fed Solution II.
 Rat 4. — Fed Solution III.

THE STABILITY of VITAMIN B₁ in ACHLOR-
HYDRIC GASTRIC JUICE.

The following investigation was made in an attempt to determine whether rapid deterioration of vitamin B₁ occurred in the achylic stomach, using the "Red growth" rat test as criterion. Four young rats from healthy litters were fed on B₁ free diet, advocated by Birch and Harris.^{283A} This was made up of (in parts) Sugar, 60; Arachis oil, 15; light white casein, 20; salt mixture, 5; autoclaved marmite (1 hour, 15 lbs., pH10), 6; cod liver oil 1 drop per day. On this diet they subsisted until there was a general decline in weight, but the investigation was begun before polyneuritic symptoms were allowed to develop.

Fasting-juice was withdrawn from the stomach of a patient suffering from duodenal ulcer; the free acidity was 30, total acidity 42 (N/10 NaOH). To 10 c.c. acid juice were added 50 international units of vitamin B₁ ("Betaxin").

Fasting-juice was withdrawn from the stomach of a patient suffering from pernicious anaemia and subacute combined degeneration (Case No. 18). There was absence of free acid, and a total acidity of 4 (N/10 NaOH). To 10 c.c. were added 50 international units of vitamin B₁ ("Betaxin"). This was divided into two equal portions; to one portion were added 2.5 c.c. N/10 HCl.

The three solutions were incubated for twelve hours at body-temperature and on removal diluted with distilled water so that 1 c.c. diluted solution contained 1 international unit of vitamin B₁. The solutions were numbered 1, 2 and 3 and kept in stoppered sterile flasks.

Sol. I. 1 unit vit. B₁ in acid gastric fasting-juice plus water to 1 c.c.

Sol. II. 1 unit vit. B₁ in achlorhydric fasting-juice plus water to 1 c.c.

Sol. III. 1 unit vit. B₁ in achlorhydric fasting-juice, rendered acid, plus water to 1 c.c.

The rats were kept on their basal diet. Rat I was given Sol. I, Rats II and III were given Sol. II and Rat IV was given Sol. III. 1 c.c. of solution was added to a small amount (about 3 c.c.) of drinking water daily, which was contained in an inverted narrow-stemmed flask fixed to each cage; fluid had to be sucked from the neck of the flask. No further supply of water was given until the solution in the flask (containing 1 unit of vitamin B₁) had been drunk. Each rat occupied a separate cage and coprophagy was prevented by the use of convex metal floors in the cages by which faeces slid into inaccessible side gullies.

The effect on growth is expressed graphically in Chart II. It might be anticipated that if the vitamin was detrimentally affected in achlorhydric gastric juice, the resulting effect of such vitamin-containing juice would be less favourable to the growth of rats. It will be seen that there was no material difference in the growth (weight) of rats II and III compared with rats I and IV. No. III did not increase in quite the same proportion as I, of similar initial weight, after six days, but this represents a much longer time than would be allowed for the absorption of the vitamin in the normally-functioning alimentary canal. The subsidence of the growth curves of rats II and III about the 25th day was thought to be due to deterioration of the No. 2 solution (Solutions 1 and 3 were acid).

DISCUSSION.

From the wealth of available data, the disease Beri-beri has been shown to be fundamentally due to a deficiency of vitamin B₁. Other deficiencies of all kinds may cause variation in the clinical picture but the gross deficiency is that of the antineuritic vitamin. On this belief therapy has been based, and with success. On the same belief the original investigations into the aetiology of alcoholic and gestational neuritis were instituted, and these conditions compared with beri-beri. Inasmuch as a knowledge of the vitamin itself has a wider application than that of beri-beri, it would, I think, be wiser to think of clinical complexes in terms of "degrees of vitamin deficiency", than in terms of beri-beri, which is purely the most extreme expression of a vitamin B₁ deficiency clinically recognised. Short of that extremity many "states" of inadequacy may exist and may be difficult to identify or classify in terms of deficiency of vitamin B₁ or any other individual vitamin; other minor deficiencies may be superimposed, and confusion added by toxæmias of various origin. These constitute the minor degrees of ill-health. As so little is known of the actual human requirement of accessory food factors, then in

the absence of any direct qualitative or quantitative test, the therapeutic response to such a preparation as parenteral vitamin B₁ may constitute the principal evidence of a lack or deficiency of this factor.

In the majority of the cases under discussion, polyneuritis was but a part of the clinical picture. We were not dealing here with gross beri-beri. It is therefore of major importance to determine, if possible, whether the nervous phenomena in these cases were related at all, to a vitamin B₁ deficiency; and whether such deficiency assumed an importance equal to, or greater than, any other pathological stigmata that were present.

These questions may be decided by determining whether - (1) aetiologically, (2) clinically, (3) metabolically, and (4) therapeutically - the manifestations were consistent with those of varying degrees of vitamin B₁ deficiency. (As there were no fatal cases, the pathological findings cannot be discussed.)

(1) Aetiologically. Was there an undoubted dietary inadequacy of vitamin B₁ over a sufficiently prolonged period to produce deficiency symptoms? Fraser and Stanton showed that in diets so manifestly deficient in vitamin B₁ as polished rice, beri-beri

did not develop for 89 days; this must therefore constitute the minimum period of inadequacy. As the standard of adequacy, Cowgill's prediction method of calculation is the only available one for evaluating man's requirement. In most cases it was not possible to obtain accurate dietary details over a period of months. Cases 6, 7, 8 and 9 had subsisted on manifestly poor diets. In all other cases the diets were not considered deficient over a sufficiently prolonged period, or were not capable of detailed calculation. In many - Nos. 10, 12, 13 and 18 particularly - the diets were of high value. Cowgill's VIT/CAL ratio was calculated in several cases. In Case 8, it was below the standard of adequacy over a prolonged period and according to this prediction, polyneuritic symptoms of deficiency had appeared. But Cases 9, 12, 13, 14 and 17 were found to have VIT/CAL ratios above the standard of adequacy for their body weights; symptoms due to deficiency should not have appeared - yet these patients had polyneuritic symptoms, not differing materially from other cases. Could these be due to a vitamin B₁ deficiency when no determinable deficiency was present in the diets? In brief, polyneuritic symptoms were present in ten cases out of fourteen in

which there was no prolonged dietary deficiency. (I cannot discuss Cases 1 to 5 as no dietary details were available.)

Were there any other factors of toxic or infective nature capable in these cases of causing polyneuritis?

No patient had a febrile illness. Diabetes was associated with five cases; alcoholism with three cases; anaemic conditions with nine cases; dysentery with one case. Case 19 had had specific arsenical and bismuth therapy but nervous symptoms had preceded it. In Case 18, carbon bisulphide and benzene poisoning had been early suspect but had been eliminated. Constipation had been present in nearly all; in three cases there was oral sepsis, but not in others of equally marked polyneuritic severity. Otherwise there was no history of exposure to lead, arsenic, diphtheria, mercury or other recognised "causes". Reviewing these factors, alcohol has been shown to possess no direct neurotoxic effect; many diabetics do not develop polyneuritis, nor does control of the diabetes necessarily affect nervous symptoms. In anaemia, whether simple or pernicious, no true causal factor has been implicated. Dysentery has been shown to be a precipitating factor in beri-beri rather than a true cause

of symptoms. And hypothetically to implicate the toxins of constipation and oral sepsis is ultimately to beg the question as to their direct neurotoxic effect. Three of the cases of diabetes had been under excellent control by diet and insulin for a prolonged period without amelioration of neuritic symptoms. Therefore to ascribe the polyneuritis to dietetic, toxic, alcoholic, diabetic and anaemic factors, which were not present in other cases of polyneuritis showing similar symptoms, could not provide the ultimate or satisfactory answer as to the fundamental aetiological denominator.

(2) Clinically. Were the polyneuritic phenomena in these cases consistent with a vitamin B₁ deficiency, as recorded in other cases, particularly beri-beri? Were there other symptoms and signs also referable to such a deficiency?

The most consistent finding in beri-beri has been seen to be degeneration of peripheral nerves and their terminations at the neuromuscular junctions. The clinical phenomena in beri-beri are capable of close relation with this pathology. The more extensive changes in the spinal cord and brain have not been so consistently found as to be considered pathognomonic

of a pure vitamin B₁ deficiency. The peripheral nerve changes, on the other hand, are consistent early findings in both experimental and human deprivation, and I propose to confine myself to these phenomena.

In all cases, some degree of peripheral neuritis was believed to exist, and the elicitation of the signs was corroborated in each case by other clinicians in the various hospital wards. In Cases 3, 4 and 5 of Dr Russell's cases, and 16, 17, 18 and 19, signs of peripheral nerve degeneration were thought to be co-existent with spinal cord degeneration. In Cases 7, 8, 10, 11, 12, 13, 14 and 15 the clinical picture was typical of polyneuritis in varied degree and extent, but always attended in the affected limbs by subjective phenomena of numbness, tingling, cramps, etc., and objectively by sensory loss or impairment, deep tenderness, diminished or absent reflexes, muscular weakness, and in two cases by foot or wrist drop. Cases 6, 9 and 15 were not "typical" cases of polyneuritis, but by reason of altered reflexes and slight degrees of sensory impairment could be grouped into that "doubtful" or "rudimentary" state, already described, characteristic of a partial vitamin B₁ deficiency, not sufficiently severe as to impress itself upon the patient's

consciousness, but objectively capable of discernment.
(See page 140.)

With respect to cardiac manifestations, associated with gross degrees of vitamin B₁ deficiency, (right-sided dilatation and oedema of the cardiac muscle) in no case could cardiac phenomena be ascribed specifically to any avitaminotic factor. Case 9 had mitral incompetence and a systolic murmur quite compatible with any pronounced anaemic state; Case 10 had slight cardiac enlargement, a history of transient degrees of oedema of the hands, palpitation on slight exertion, and oedema of the feet and ankles on admission - findings compatible with a vitamin B₁ deficiency but not specifically so; on the other hand there was no rheumatic or other history, and the cardiac phenomena were associated definitely with his present illness. In other cases, the degrees of tachycardia, palpitation and objective findings were not outstanding and were always equally capable of association with anaemia or other co-existing conditions.

With respect to gastro-intestinal symptoms, however, there was a constant, almost inevitable, association. We have seen that in beri-beri - whether occurring alone or in association with tropical or other diseases,

gastro-intestinal manifestations - anorexia, nausea, vomiting, diarrhoea or constipation - are constantly a feature of the clinical picture. In both experimental and human cases, the deprivation of the antineuritic vitamin is frequently manifested in loss of appetite, emaciation and other gastro-intestinal symptoms before the onset of polyneuritis. Secondly, in cases of partial deficiency the occurrence of a gastro-intestinal aspect of any origin has, as we have seen, frequently precipitated a condition of true deficiency; gestational polyneuritis, dysenteric and "alcoholic beri-beri" are outstanding examples of this.

In every case without exception in the present series, there was a history of gastric disturbance, symptoms of anorexia, nausea, flatulent dyspepsia and constipation being predominant. In Case 1, dysentery figured in the history; in five cases there was a prodromal history of gastritis and vomiting; Case 6 was suspected of gastric carcinoma; in Case 8 the symptoms were intensified following gastritis; in three cases alcohol could be implicated as the cause of gastric symptoms; in Case 10 there was a very prolonged history of chronic gastritis, and the present polyneuritic illness was immediately preceded by acute

gastritis, vomiting and diarrhoea. Increasing degrees of anorexia were constant subjective admissions. Objectively, the chronic nature of the dyspepsia repeatedly found corroboration in the exhibition of a flabby, bald tongue, with papillary atrophy.

Gastric Analysis. In Dr Russell's five cases, three had gastric anacidity; the first two cases were not analysed. In the remaining 14 cases, gastric analysis by fractional test meal was performed in all but one case. Eleven out of thirteen showed complete achlorhydria.

Clinically, therefore, whilst cardiac manifestations were inconspicuous, the nervous and gastrointestinal phenomena in these cases bore features in no way dissimilar from those described as constant manifestations of vitamin B₁ deficiency states.

(3) Metabolic or Bio-chemical findings. We have seen that vitamin B₁ is a catalyst, and concerned in the oxidation of certain bi- or end-products of carbohydrate metabolism to which the name bisulphite-binding substances has been given. A gross accumulation of these substances in the blood has hitherto been identified only in gross B₁ avitaminotic states, while in lesser

degrees of deficiency, the amounts approximate to normal levels. In experimental and gross human B₁ deficiency states, there is a marked and rapid reduction in the amounts of these B.B.S. substances following administration of the vitamin. The literature reveals, however, that there are wide limits of normality, that the effect of administering vitamin B₁ on these "normal" levels has not been adequately investigated, and thirdly, that this recent study has not been applied to polyneuritic conditions which might be due to minor degrees of vitamin B₁ deficiency.

In order to test the applicability of this biochemical test, the blood level of bisulphite binding substances was determined in four cases, before and after the administration of parenteral vitamin B₁. In all four cases, the initial level was within the reported normal limits, but there was a distinct fall following vitamin B₁; in Case 9 (anaemia) from 2.87 to 2.01; in Case 18 (nervous lesions of pernicious anaemia) from 2.60 to 2.01; in Cases 12 and 13 (diabetes) from 2.06 to 2.02, and 3.03 to 2.51 respectively, (expressed as mgms. B.B.S. per 100 grams blood).

It is a matter of regret that the estimation of bisulphite binding substances was not made in more cases,

but its possible significance was not appreciated sufficiently early. The B.B.S. reduction in four cases only may not provide convincing evidence of the pathological nature of these substances in such cases; but in that there was a co-incident clinical improvement demonstrable, and also a reduction similar in type (though admittedly not of the same degree) as in pronounced vitamin B₁ deficiency states, the findings have, I venture to think, a significance referable to the administration of vitamin B₁.

(4) Therapeutic results of parenteral vitamin B₁.

It has been convincingly and repeatedly shown that where a true vitamin B₁ deficiency exists, the administration of the vitamin - provided it is given in sufficiently adequate doses, and its rapid permeation to the tissues beyond question - is followed by amelioration or cure of the peripheral neuritis (or paralysis in the pigeon and certain animals), and usually improvement in other symptoms such as loss of appetite, and reduction in the degree of cardiac dilatation if this exists. Further improvement is probably related to increased intake of food, better circulation, etc., and secondary physiological betterment. We have seen that the rapid nervous improvement in the periphery is

in accord with the relief of the biochemical lesion, and the first sign of improvement is therefore to be sought in improved condition of nervous impulses in the peripheral nerve terminations. Secondly, as Russell has pointed out, the shortest peripheral nerves appear to recover most rapidly, with the result that the areas of sensory loss in the limbs express returning sensation by a "shrinkage" or recession distally towards the periphery. Thirdly, the improvement must inevitably be commensurate with the chronicity of the lesions and the degree to which true degeneration has taken place.

Numerous opinions are held as to the parts played in subacute combined degeneration and other cord lesions by vitamins other than B₁, and these have been briefly referred to. . But there is, as yet, almost unanimity of opinion that in beri-beri, the peripheral nervous lesion is due to deficiency of the antineuritic vitamin, though the acuity or chronicity of the lesions may be influenced by other co-existing avitaminoses.

I propose, therefore, to use as criteria of therapeutic response to parenteral vitamin B₁,^{only} those manifestations of nerve injury or impaired conduction which are accepted as being due to a deficiency of this factor. . .

Dr Russell has described in the first five cases the results of vitamin B₁ administration, and the rapidity with which some degree of improvement was manifested.

In my own series, Cases 11 and 15 showed a dramatic response; the former lost in a few days the numbness and tingling from his fingers which had been present for three years, and objectively sensory appreciation quickly reappeared; this improvement could not have been due to relief of glycosuria, as the symptoms had been present in spite of being sugar-free for long periods previously. In Case 15, the dramatic response was hardly due to an improved blood condition, as the symptoms and signs were still present in spite of a blood picture which was little short of normal. Case 10, who was reminiscent of true beri-beri, showed better objective sensory appreciation almost at once, and later by return of reflexes; he was able to walk in three weeks after bilateral foot drop, and it is doubtful whether any other forms of treatment would have accomplished such an effect so rapidly. Case 8 showed much slower improvement, and this was probably due to his receiving parenteral injections of 50 units of the vitamin, in comparison with the 400 to 1000 units

administered to later patients. Case 9 showed no return of absent reflexes, but there was a marked return of appetite and much reduced sensory loss after the first few injections. Case 7 showed improvement subjectively and rapidly by diminished tingling and numbness in the fingers after months' duration, and improved appetite. The improvement in Case 14 (alcoholism and diabetes) is difficult to explain precisely; here there was removal of a noxia - alcohol - and control of the diabetes; it was difficult to secure co-operation in defining sensory improvement, and amelioration was slow following comparatively small injections of vitamin B₁ (50 units); yet after three weeks there was a return of absent reflexes and decreased severity of muscle cramps. Secondly, although his second visit to hospital was characterised by coma and more severe manifestations of polyneuritis than on his preceding visit, the addition of parenterally administered vitamin B₁ to treatment produced a more rapid and satisfactory improvement. In addition, it may be significant that he required smaller doses of insulin to control his carbohydrate metabolism when vitamin B₁ was co-incidentally used in therapy. Cases 12 and 13 (diabetic neuritis) showed at the end of a

week's (daily) treatment, improvement in sensory peripheral conduction, diminished tingling and numbness, and relief from painful night cramps which had made the nights a misery.

In the cases of pernicious anaemia with nervous lesions, the improvement was much less marked; but according to criteria used, there was improvement in the lessening of "pins and needles" and tingling sensations, and objective improvement demonstrable in the return of sensation to areas of sensory loss. Any betterment in these cases of pronounced degeneration can only be gauged by observing them over a prolonged period. Case 19, however, demonstrates the immense improvement possible in this condition if treated early. Here there were no signs of degeneration other than those affecting peripheral nerves and the posterior columns. It is true that liver therapy was combined with vitamin B₁, but I venture to think that the relief from nervous phenomena was much more rapid and pronounced than would have been obtained by liver alone. From a condition bordering upon helplessness, this patient regained sensation, almost lost his cramps, recovered his reflexes without developing a "Babinski" sign, and was able to discard his "sticks" and walk two miles in a

few months; the peripheral sensory improvement was demonstrable after a few injections of vitamin B₁ (400 unit doses) before the blood condition had made any pronounced progress. I regard this case as a striking example of the improvement possible if the nervous lesions of pernicious anaemia can be treated before irreversible degeneration of nerves and tracts has occurred.

Improvement in appetite has been referred to. Cardiac conditions were not severe, but in Case 10, support is lent to the diagnosis of beri-beri by the fact that without specific cardiac treatment, other than rest, the cardiac enlargement (a product of the illness) decreased to normal before leaving hospital.

The reduction of the amount of bisulphite binding substances following vitamin B₁ treatment in four cases has also been referred to.

I unhesitatingly conclude, therefore, that judged according to criteria consistent with the action of vitamin B₁, the above cases showed therapeutic responses which could be directly attributed specifically to the administration of this vitamin. A review of these cases, therefore, indicates that clinically, therapeutically and to a minor degree, metabolically,

they are in close agreement with degrees of B₁ vitamin deficiency states. But not aetiologically! There was no consistent dietary inadequacy.

A study of other diseases reveals, however, that nutritive essentials may not be absorbed in spite of dietary adequacy if gross gastro-intestinal derangement exists. Pernicious anaemia, idiopathic hypochromic anaemia, sprue, coeliac disease, idiopathic steatorrhoea, and alcoholic pellagra, are but a few of this group. We also know that certain substances, e.g. insulin and other hormones, are destroyed in the bowel, and their successful function depends on parenteral administration.

If it be true that "where there is dyspepsia there is gastritis", then the series of cases recorded here affords examples of gastric derangement. The finding of achlorhydria in eleven out of thirteen cases where gastric analysis was undertaken affords additional evidence of some degree of atrophic change in the gastric mucosa. In the two cases where secretory activity was found, gastritis and diarrhoea preceded the onset of symptoms in one of the few patients who had demonstrably subsisted on an inadequate diet for months; in the other case there was a gastro-intestinal upset

consequent upon whisky and methylated spirit drinking. In the case in which gastric analysis was not practicable, the nature of the flatulent dyspepsia and the papillary atrophy of the tongue strongly suggested an achlorhydric state.

The consistent response to the parenteral administration of the vitamin compared with the poor response to oral dietary administration was also strongly suggestive of malabsorption, or destruction of the vitamin in the alimentary tract. Dr Russell's first case exemplifies the significance of absorption; in spite of taking adequate diet and marmite daily, tingling in the extremities appeared at about ten day intervals if vitamin B₁ had not been administered parenterally.

Previously in this thesis I have referred to the consistently occurring gastro-intestinal symptoms in cases of polyneuritis recorded by Strauss, Perkins, Wechsler and others. Harris²⁸⁴ also drew attention to this association and named the condition "chronic progressive (endotoxic) polyneuritis". In 1936, Douthwaite²⁸⁵ noted polyneuritis occurring in association with cases of gastric carcinoma, pyloric obstruction and achlorhydric anaemia, and suggested the name "Gastrogenous polyneuritis" for such cases.

It is easy to presume a condition of malabsorption, but difficult to prove in the absence of direct tests. Though somewhat irrelevant at this stage, may I be permitted to state the nature of an investigation the results of which arrived too late to include at an earlier stage. L. G. Harris²⁸⁶ recently devised an indirect method of evaluating the dietary adequacy of vitamin B₁ by estimating the amount of the vitamin excreted in the urine; this is accomplished by the Harris "rat-bradycardia test", fully described by the author. Over a large series of healthy cases, it has been found that 5-8% of the ingested vitamin is excreted in the urine. In ordinary good diets, this represents an excretion of 12 to 35 international units in the urine per day. Vitamin decreases in the diet are followed by proportional decreases in the urinary excretion, and according to Harris (a) daily excretion of less than 12 I.U. raises the presumption that the diet contains less than the normal allowance of vitamin B₁, and (b) in actually developed avitaminosis (beri-beri) in man, vitamin B₁ may cease to be excreted in the urine in appreciable amounts (< 2.5 I.U. daily).

Dr Harris kindly consented to estimate the urinary excretion of vitamin B₁ of a patient in whom absorption

To page 8. 295.

<u>Name</u> McCulloch,					
(The Royal Infirmary, Edinburgh).					
(1) <u>Date</u>	(2) <u>Specimen</u>	(3) <u>Volume</u>	(4) <u>Days</u> <u>cured</u>	(5) <u>I.U./</u> <u>day</u>	(6) <u>Remarks</u>
18.2.37	I	1200	-	-	Specimen arrived broken
19.2.37	II	1320	1, 2	4.0	} Low B ₁ output suggests inadequate intake
20.2.37	III	1320	1, 1	2.6	
21.2.37	IV	1040	1	4.1	
22.2.37	V	1380	-	-	Not sent
23.2.37	VI	1920	9, 10	45.6	[Betaxin] 1000 I.U. in-
24.2.37	VII	*	6	*	jected
25.2.37	VIII	*	3, 5	*	

Illustrating diminished urinary secretion of
Vitamin B₁ in a patient having 280 I.U. orally per day.

was suspect on account of achlorhydria. Case 9 was chosen for investigation. She was kept on a strict diet of the following constituents (the vitamin B₁ being expressed in mgm.-equivalents in parentheses): Oatcake, 120 g. (1440), Milk, 100 g. (360), Cream, 75 g. (315), Bacon, 60 g. (1080), Lean meat, 60 g. (420), Fruit, 100 g. (300), Eggs, 100 g. (550), Vegetables and Tomatoes (1100 mgm.-eq.), making a vitamin B₁ total per day of 5565 mgm.-eq. or roughly 280 I.U. An excretion of 5-8% of this amount would result in the recovery from the urine of 14 to 22.4 I.U. of vitamin B₁ daily. Yet Harris' report shows that for three successive days the amounts recovered were 4, 2.6 and 4.1 I.U. - "suggesting inadequate intake". After the injection of 1000 units of the vitamin, the output rose to 45.6 I.U., the specimen containing this being capable of "curing" a rat for 9-10 days; on the two following days the output apparently rapidly diminished, the capacity for "cure" diminishing to 6, and 3-5 days.

This appears to indicate that in spite of a diet adequate in vitamin B₁ content, some destructive or malabsorptive factor was at work; whether the surplus vitamin was excreted by the bowel, or destroyed is not known, but research is in progress to determine the

fate of the vitamin.

These features taken collectively indicate that vitamin B₁ deficiency states are not only dependent on adequacy in the diet, but on the capacity of the alimentary tract to absorb. They also explain the rapid and certain action of the vitamin when administered parenterally and the failure in many cases of oral administration. In addition, these findings help to explain why ten out of fourteen cases developed symptoms suggestive of vitamin B₁ deficiency in spite of diets adequate in this respect.

It therefore becomes possible to state with respect to the cases investigated:-

1. Aetiologically, there was a deficiency of vitamin B₁ either (a) in the diet, or (b) conditioned by gastro-intestinal derangement, the outstanding manifestation of which was achlorhydria, presumably resulting in mal-absorption of the vitamin.
2. Clinically, the symptoms and signs (polyneuritis) were indistinguishable in type from those described in B₁ vitamin deficiency states, of which beri-beri is the severest form.
3. The biochemical lesion was suggestive of that described in vitamin B₁ deficiency.
4. The therapeutic parenteral administration of vitamin B₁ was successful in relieving symptoms of peripheral neuritis, in reducing the amount of bisulphite binding substances in the blood in four cases, and in producing to a less extent, changes in anorexial and

cardiac manifestations capable of correlation with the action of the vitamin.

5. It is therefore concluded that these cases represented, inter alia, varying degrees of vitamin B₁ deficiency states.
-

It now becomes pertinent to discuss certain factors which have arisen in the light of the above findings.

Cowgill's prediction formula. Whilst this may represent a satisfactory method of estimating a dietary adequacy, where this is the only point in question, it is doubtful, for two reasons, whether it is capable of practical application in all cases of suspected vitamin B₁ deficiency:

1. It requires the furnishing by the individual concerned of all dietary details, qualitatively and quantitatively, over a prolonged period of time (at least 90 days); very few patients are capable of supplying such detailed information. (In the case of diabetics an exception is made, as standard measured diets are employed. But the suggestion that polyneuritis is due in diabetics to the employment of diets deficient in vitamin B₁ foods was not found in the

present series of cases. The R.I.E. diets prescribed by the Dietetic Department were found on detailed examination to be more than adequate in vitamin B₁.)

2. Dietary adequacy in terms of vitamin B₁ does not constitute a safeguard against beri-beri or other states of deficiency unless the various organs concerned are capable of absorbing and utilizing the vitamin.

From the results of the present investigation it would appear that the vitamin B₁ requirement of man is determined not only by his food intake and body-weight, but by his capacity to utilize the vitamin ingested in his diet.

The Neuropoietic factor. Certain observers have suggested that vitamin B₁ represents an extrinsic factor and that the healthy gastric mucosa furnishes an intrinsic factor, the interaction of the two being essential for the continued nutrition of the nervous system. I can find little confirmation for such an hypothesis; (a) vitamin B₁ acts both in vitro and when parenterally administered, without passing through the stomach; (b) it is excreted as vitamin B₁ in the urine and can be extracted as such. (c) Vitamin B₁ is not the only factor incriminated in the production of nervous degeneration, and its action appears to be through the

medium of metabolism rather than a direct neurological one; (d) there is evidence that even in cases of doubtful assimilation, the giving of massive doses of the vitamin allows of absorption, analogous to that observed following large doses of calcium or iron; and (e) its apparent failure of function is capable of explanation by destruction, or malabsorption in atrophic conditions of the upper alimentary tract such as are encountered in achylia gastrica; there appears to be no valid reason for invoking the absence of hypothetical neuropoietic factors to explain nervous degeneration.

Does Vitamin B₁ undergo deterioration in the achlorhydric stomach? Since the vitamin is resistant to acids but not stable in alkalies, the possibility that the pH of the gastric and duodenal contents may influence its stability is conceivable. The investigation described on page 275 does not indicate any rapid deterioration of the vitamin in the achylic fasting-juice of a patient suffering from pernicious anaemia. On the other hand, the vitamin concentrate used in this experiment may not react in the same manner as the vitamin contained in foodstuffs; and the amount used (50 units per 10 c.c. juice) may have been sufficiently concentrated to counteract any deleterious action of

the fasting juice. Until more is known of the locus of absorption in the bowel, many of the problems of absorption will remain undetermined.

The correlation of the bio-chemical and peripheral nervous lesions. While dogmatic conclusions are not yet justifiable, certain tentative suggestions may be made regarding the progressive nature of nervous lesions (sequelae to polyneuritis) compatible with the action of vitamin B₁. A deficiency of the latter results in the accumulation of certain metabolic end-products; from our knowledge of the metabolism and combustion of carbohydrates, these metabolites are probably in excess in muscle tissue. In fact Platt and Yang have directed attention to the fact that in beriberi (as in lead poisoning) active and fatigued muscles are the first to show the typical phenomena. This interrupted metabolism at the neuro-muscular junction will presumably affect the conducting power of the nerve-fibril first and foremost and at its most susceptible point - where it is unprotected. This is in accord with the early nervous phenomena - tingling and other paraesthesia. The rapid clinical response following administration of the vitamin is also capable of explanation by this hypothesis - a return of normal

metabolic function, and a rapid return of nerve-function; this would explain the dramatic flight of the pigeon a few hours after paralysis, the recovery of the limb paralysis in the B₁ avitaminotic dog, and in the human being, the disappearance of paraesthesia after a few days of parenteral injections. To me, this action finds an analogy in the relief of diabetic coma (again a metabolic condition) by the prompt administration of insulin. As Peters has stated, there is no need to invoke the action of toxins to explain these phenomena; they can be rationally explained by the interruption of the normal metabolic process of the cell. If, however, this condition is unrelieved, then the nerve-myelin may become disintegrated and true degeneration begin, again most marked at the nerve termination. Thirdly, as shown by Woollard, the degeneration may now ascend proximally with true axonic degeneration. At this stage, the nerves may conceivably be affected by other noxia of metabolic or toxic nature.

Consider in the present series, Cases 6, 15, 19, 18 and 17. In all five cases we have an underlying deficiency state with an atrophic gastritis and achlorhydria. In the first case the signs are those of slight anaemia, and nervous phenomena in the

rudimentary stage - slight sensory loss and diminished reflexes. In Case 15, there is a pronounced anaemia showing a hint of transition into a pernicious type, and more definite sensory impairment in the extremities. Case 19 has developed manifest pernicious anaemia, and the peripheral nerve degeneration is now combined with manifest degeneration in the posterior columns of the spinal cord. No. 18 has pernicious anaemia very resistant to treatment, complete atrophy of the tongue papillae with absolute loss of taste, and degeneration of peripheral nerves, posterior columns, and now to a slight extent the lateral columns. Whilst case 17 has all these stigmata, with diabetes included and the lateral columns of the cord so severely attacked that her condition is irreversible and, from a curative point of view, hopeless. Yet in the first two, and possibly the third case, we are dealing with phases in a process still reversible in nature, provided treatment is adequate and thorough.

I do not infer that all degenerative lesions of the nervous system originate in peripheral muscle and nerve end-organs. There is reason to believe that in many cases the brain and spinal cord are first affected. But I suggest that re-investigation of metabolic

changes in muscle and in relation to peripheral nerves may eventually throw much light on certain nervous syndromes which affect both the latter, and the tracts in the spinal cord.

The Nervous System in other Avitaminoses. I

have not considered it advisable to confuse the issue by discussing the action of certain other vitamins. That other degrees of avitaminosis exist in states of B₁ deficiency is more than feasible. The detailed study of an impoverished diet usually reveals deficiencies of many vitamins, minerals and other essentials, and the resulting clinical picture will tend to ^{be} an expression of the deficiency which is most pronounced - beri-beri, pellagra, scurvy as the case may be. That mixed deficiency states are capable of clinical recognition is shown by numerous reports of pellagrous skin lesions occurring in beri-beri, peripheral neuritis in pellagra, xerophthalmia and scurvy in beri-beri, etc. The naturally occurring combination of vitamin B₁ and B₂ in food-stuffs tempts the suggestion that a pure avitaminosis of either one alone is extremely unlikely, and it is conceivable that many clinical phenomena are due to the vitamin B complex which are ascribed as specific for one or other

factor. In the present series of cases no gross lesions which could be reasonably attributed to other vitamin deficiencies were discerned clinically. But, in passing, it has been claimed that in pronounced A and B₂ avitaminoses, nervous and spinal cord degenerations have been experimentally produced. Glossitis, hypo- and achlorhydria are equally associated with pellagra, and subacute combined degeneration of the spinal cord is often a late nervous complication of the disease. A prolonged deficiency of, say, vitamin B₁ results eventually in anorexia, and apparently disturbance of the normal secretory mechanism of the stomach. The reduced intake of food will probably affect all accessory factors in time, and in addition will result in a depletion of their tissue stores, thus leading to states of secondary deficiencies. No gross manifestations of a deficiency other than the initial one may be evident, but the lack of precise identification of such states is probably due to our inadequate knowledge of their minor manifestations rather than to the possibility that they do not exist. We still suffer from lack of direct blood tests for determining the presence and quantity of vitamin factors. Until such methods are available and until the inter-relation and

interactivity of vitamins have been more fully investigated, then in conditions associated with any pronounced deficiency it would appear prudent and rational to supplement any specific additions in treatment with the provision of a diet adequate in all essential factors. The increased susceptibility to infection and toxaemias which apparently exists in states of vitamin A deficiency is a further incentive to the supplying of all essential factors in doubtful cases. In gross beri-beri in the East, it is frankly recorded that success in treatment is most regularly achieved by the supplementing of vitamin B₁ by adequate good diets.

In the present investigation, though attention was directed initially to observation of the action of vitamin B₁ without additional measures, the later provision of light but fully adequate diets was always secured.

Other Polyneuritic States.

In addition to the numerous cases of polyneuritis of obscure origin, there is a large group in which the cause is ascribed to toxic factors definitely associated with the onset of symptoms. Lead, arsenic, phosphorus, alcohol and the toxins of pregnancy belong to this

class. In the case of the latter two, we have seen that although they are definitely implicated in the production of polyneuritis, there are grounds for believing that it is the avitaminotic state produced by these noxias rather than any direct neurotoxic action they possess, which leads to the pathological changes. Though cases of lead, and other similarly "poisonous" cases were not available for study, certain suggestions appertaining to these forms and arising out of the present investigation may not be out of place.

In nearly all the cases studied, whether of obscure, alcoholic, diabetic or other origin, the most consistent finding was a gastro-intestinal derangement with achlorhydria, presumably producing a deficiency state by inhibiting digestion and absorption. In Diabetes, the polyneuritis did not appear to be associated with that condition, per se; in addition to the commonly associated metabolic defect, was the superimposed lack of a substance capable by its catalytic action of causing the oxidation of other carbohydrate metabolites. In fact it would appear that for the adequate combustion of carbohydrates both insulin and vitamin B₁ are essential. This double-deficiency may be far from the ultimate truth as an explanation of "diabetic neuritis";

but as vitamin B₁ is so closely related to carbohydrate metabolism, is it not singular that neuritic manifestations occur so frequently in diabetes - essentially a carbohydrate metabolic derangement? A vitamin B₁ conditioned-deficiency may eventually be found to have a large contributory share in diabetic polyneuritis, and routine gastric analysis in such cases may yield results no less striking than in the cases here investigated.

Just as thousands of individuals drink alcohol, encounter pregnancy, and suffer from diabetes without developing polyneuritis, so too are countless numbers exposed to lead and other poisons, and to treatment by arsenic, mercury, bismuth, gold and phosphorus without developing neuritic complications. When these do occur, they are often ascribed to the toxic effects of the specific "poison" concerned. But it cannot be the whole truth, and does not satisfactorily explain why by far the greater majority are spared the nervous complications. Alcohol attacks the gastro-intestinal tract and the liver; the products of pregnancy cause profound hyperemesis and hepatic disorder; in diabetic polyneuritis, we have found that for some reason a gastric derangement has occurred resulting in achlorhydria. And the polyneuritis associated with these conditions

has responded, to an appreciable degree, to treatment based on the assumption that a polyneuritic condition was due to either faulty intake, or faulty absorption of essential vitamin factors.

Lead, phosphorus and arsenic, when taken orally over prolonged periods are known to be associated with many profound derangements of the gastro-intestinal tract; symptoms of anorexia, vomiting, severe constipation (lead), profuse diarrhoea (arsenic), and often, in the case of phosphorus, acute yellow atrophy of the liver. I particularly drew attention to the observation that lead neuritis and weakness is most marked in muscles where there is greater accumulation of lactic acid, whether due to exercise or fatigue (page 25) and that the resulting appearance and extent of the lesions seem to depend on chemical interaction. In vitamin B₁ deficiency states there is also an accumulation of lactic acid, through the lack of the catalytic vitamin. In beri-beri also, fatigued muscles are the ones most severely affected. These observations warrant reflection. The patient with gold polyneuritis to which I referred earlier, was found to have a red, glazed tongue and achlorhydria; she therapeutically responded to generous dieting "with abundance of vitamins,

particularly vitamin B".

All these forms of poisoning have in common with alcoholic and gestational polyneuritis, and the cases investigated, invariable symptoms of gastro-intestinal (and often hepatic) derangement. If these conditions are productive of disordered states which interfere grossly with the ingestion, the digestion and the absorption of foodstuffs, and therefore of essential accessory factors, the lack of which has been shown to lead to degeneration of nerves, then the gastro-intestinal derangement may be the determining factor in that degeneration; and the avitaminotic state the common denominator to them all. The degenerative change may be the result of some direct action of the lead, or arsenic, etc., toxic only in the chemically abnormal tissue resultant upon the avitaminosis; or the interrupted metabolism of the tissue cells, or the prolonged action of metabolites and other toxins may accomplish the pathological change. Many hypotheses to explain the local damage are feasible, but none so important as the possibility that these supposedly toxic metals may only be capable of effecting nervous impairment in the presence of a deranged metabolic environment consequent upon a state of avitaminosis.

Such a conception does not belittle the importance of eliminating as speedily as possible the noxious agent, both by reason of its possible action in the tissues and its effects in prolonging the alimentary disorders. But it draws attention to, and emphasizes the necessity in all such cases for repairing such deficiencies as may exist by adequate nutrition, and in the case of peripheral neuritis, by the supplementary and parenteral administration of vitamin B₁ in large doses.

It is a matter of regret that occasion did not arise to investigate and treat such cases on similar lines to those previously discussed.

More and more evidence/^{is} yearly accumulating of the part played in the production of varied disease complexes of all kinds by derangement of the gastrointestinal tract and achlorhydric states. It is as if the hand of chronic gastritis were capable of striking innumerable chords on the key-board of bodily function with most unharmonious result.

The following concluding suggestions may therefore be offered.-

1. Many cases of polyneuritis are of obscure

origin, and many occur in which there is a patent toxic, metabolic or infective association. Though seldom conforming to the clinical picture of beri-beri in this country, the polyneuritis may nevertheless be due to a vitamin B₁ deficiency and such cases may therefore be regarded as true avitaminosis.

2. This state may be brought about in two principal ways:-

- (a) by a dietary deficient in vitamin B-containing foods over a prolonged period;
- (b) by gastro-intestinal derangements, which diminish food intake, cause mechanical loss by vomiting or diarrhoea, or seriously impede digestion and the absorption of vital essentials.

Achlorhydria is very frequently associated with such derangements and should be regarded as indicative of atrophic gastritis, and of a malabsorptive state. Gastric analysis should be made as a routine measure in all cases of polyneuritis, of whatever origin.

The achlorhydria may be congenital, the result of prolonged irritation by toxins, mechanical or other irritants, or may be itself an expression of a prolonged vitamin B deficiency. From whatever cause, persons with achlorhydria tend towards a state of partial vitamin B deficiency, and may be precipitated into a condition

of true deficiency by acute exacerbation of gastro-intestinal upset, toxic or infective illness or acute loss of appetite with diminished intake of food.

Polyneuritis may be but one of the manifestations of this derangement and other complexes, particularly of the haemopoietic system, may simultaneously develop. Polyneuritis may therefore co-exist with many and diverse pathological states, yet always be an expression of the underlying avitaminosis.

3. Polyneuritis is often associated with "specific" intoxications such as lead, arsenic, phosphorus, gold, etc. Whilst awaiting further investigation, it is not inconceivable that these substances are not themselves neurotoxic, but by causing profound gastro-intestinal derangement, with consequent malabsorption and metabolic upset, condition a state of avitaminosis. In this, vitamin B₁ may be especially implicated and the ensuing polyneuritis may be an expression of the biochemical lesion rather than a specific neurotoxic effect of the intoxicant concerned. Such a process has been demonstrated in the case of alcohol and the "toxins" of pregnancy.

In cases of diabetic polyneuritis, a similar vitamin B₁ deficiency may play a contributory role,

due not so much to dietary inadequacy but to gastrointestinal disorder with which achlorhydria has been found to be commonly associated.

4. Investigated cases of polyneuritis have been found to show agreement with the polyneuritis associated with vitamin B₁ deficiency (as in beri-beri), aetiologically and clinically, and, to a slighter degree, to exhibit specific biochemical changes comparable with such a deficiency. Support is lent to this diagnosis by the response obtained to intensive vitamin B₁ therapy, such response being consistent with the known action of the vitamin in the polyneuritic manifestations of beri-beri.

5. Treatment by vitamin B₁ preparations may be.-(a) prophylactic, (b) curative.

Prophylactically, it may be used in all cases of under-nutrition, pregnancy and where for any reason there is a prolonged diminished food intake, or reason to suspect impaired gastric function. Its importance may with advantage be stressed in ordinary diets; there is reason to believe that many people subsist on foodstuffs deficient in this factor.

Curatively, the best results are obtained in cases

of peripheral neuritis during the early stages when the process is more metabolic than pathological, and at a "reversible" phase. Even in cases of true degeneration, its administration may be followed by arrest of the process, and many cures with the return of normal nerve conduction have resulted.

Though abundant supplies of vitamin B₁ should be added to the diet, the parenteral method of administration offers many advantages; larger doses are possible, speedier effect is obtained, the intake is not dependent on appetite and the vitamin is not subjected to destructive or malabsorptive influences in the alimentary tract. Parenteral injection may be the only successful method of administration in severe gastro-intestinal conditions. Injections of 1000 international units for a few days, followed by 500 I.U. daily are recommended, and no ill effects have been observed.

6. In poor, inadequate diets, and in gastro-intestinal conditions, many deficiencies other than vitamin B₁ may be assumed. The resulting disease complexes may be the expression of primary, secondary and mixed deficiency states. For these reasons, in cases of polyneuritis, in addition to vitamin B₁, a diet rich in proteins, minerals and all other vitamins should be

provided. Anaemic conditions and their co-existent nervous lesions appear to be the expressions of multiple deficiencies; as peripheral nervous degeneration appears to figure almost constantly in these complexes, adequate parenteral administration of vitamin B₁ should be added to other essentials at the earliest stage possible.

7. The diagnosis of "polyneuritis due to vitamin B₁ deficiency" should not be rejected on account of recognised adequacy of this factor in the diet. The high incidence of gastro-intestinal disorders and secretory defects suggests that vitamin B₁ deficiency is more frequently due to inadequate absorption than to a diminished intake of this factor in the diet, in this country, and probably in most temperate zones.

SUMMARY.

1. Fourteen cases exhibiting signs of peripheral nerve degeneration, have been studied; five cases treated by Dr Ritchie Russell have also been included.
2. A deficiency of vitamin B₁ of varying degree was found to be concerned:-
 - (a) By dietary deficiency;
 - (b) by gastro-intestinal derangement conditioning a state of deficiency;
 - (c) by response to specific treatment by parenterally administered vitamin B₁.
3. Achlorhydria was found to be an important aetiological factor in fourteen cases.
4. The most rapid response to treatment was obtained by parenteral injection of the vitamin; 1000 international units for three consecutive days followed by 500 international units per day, gave eminently satisfactory results.
5. As other dietary deficiencies are frequently concerned in the clinical phenomena of these cases, a diet adequate in all respects was prescribed.

In conclusion, I wish to express my sincere thanks to the many Physicians of the Edinburgh Royal Infirmary for their invaluable help in this study: to Dr Fergus Hewat, Professor D. M. Dunlop and Dr Lamb for allowing me free access to cases; to Dr W. Ritchie Russell for the privilege of collaboration in this study and for his courtesy in placing the reports of five cases at my disposal; to Dr C. P. Stewart and his staff in the Biochemical Department for estimating Blood Bisulphite-binding substances in four cases; to the Sister and staff of the Dietetic Department who assessed, in detail, a series of diets; to Dr J. Croom and Dr Lees, who supplied the rats used experimentally and to Mr Johnson, who supervised their feeding; to Dr Leslie J. Harris of Cambridge University, who carried out the series of tests of Vitamin B₁ excretion; and lastly, my grateful thanks to Miss Charlton of the Central Medical Library, who generously supplied me with literature and translated many important reports for me.

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